Long term outcome of COPD

2022 . 3 . 5
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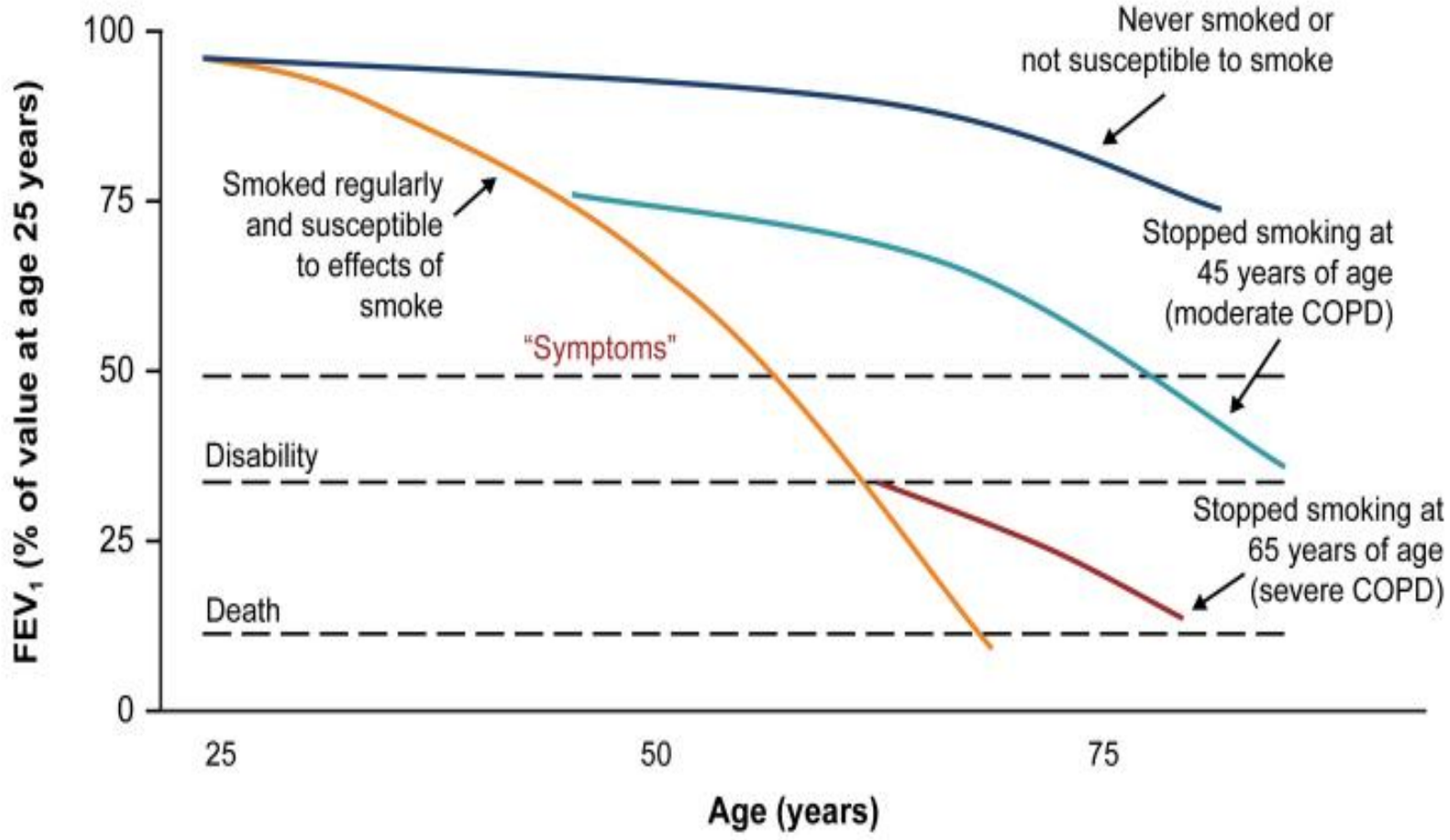
Content

- Introduction
- Pulmonary outcomes
- Extrapulmonary outcomes
- Mortality : COPD related, all cause
- Prediction of prognosis

Content

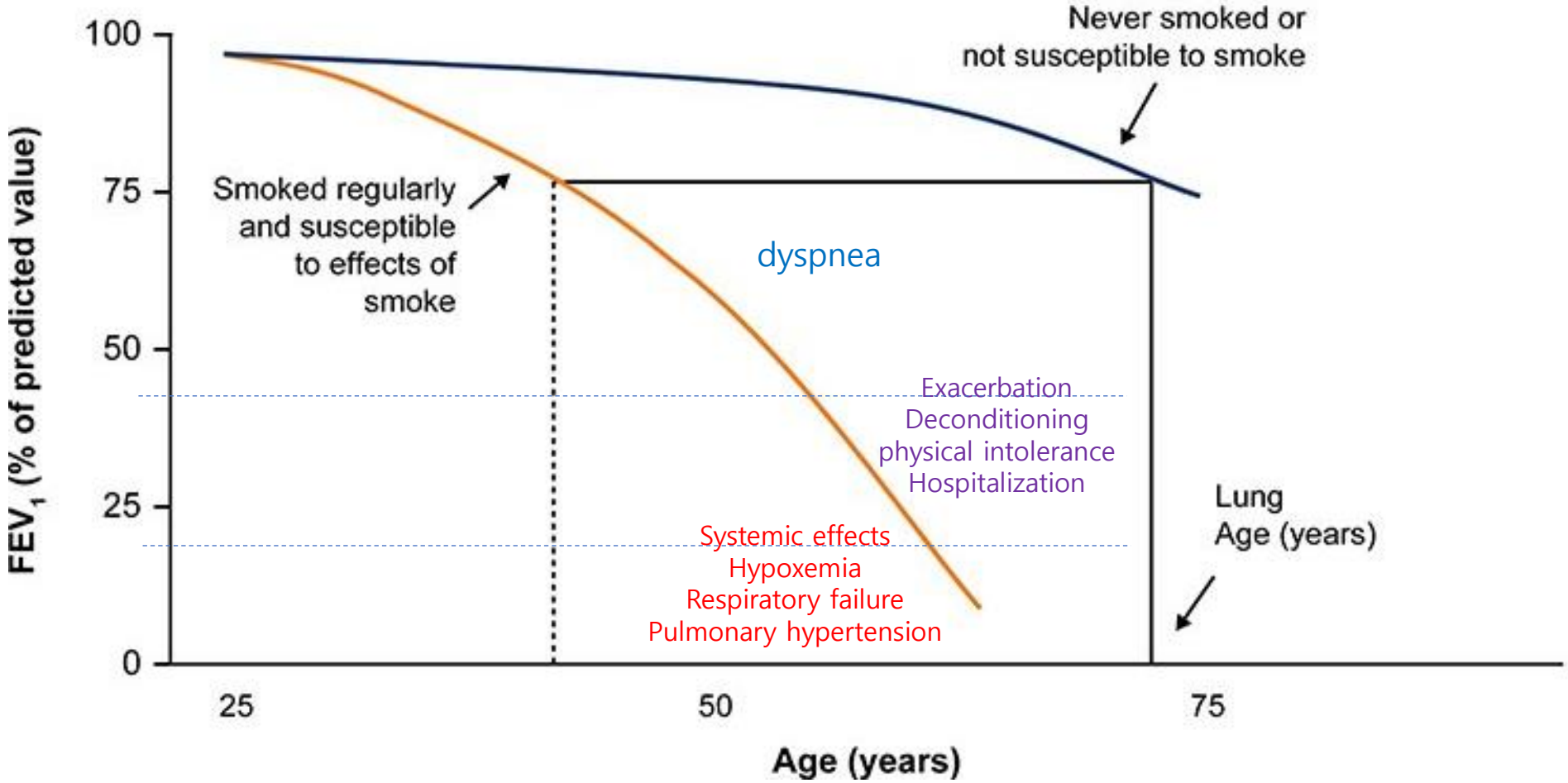
- **Introduction**
- **Pulmonary outcomes**
- **Extrapulmonary outcomes**
- **Mortality : COPD related, all cause**
- **Prediction of prognosis**

COPD is progressive disease



Adapted with permission from Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645–1648
Yawn et al. Int J Chron Obstruct Pulmon Dis. 2021:16 289–299

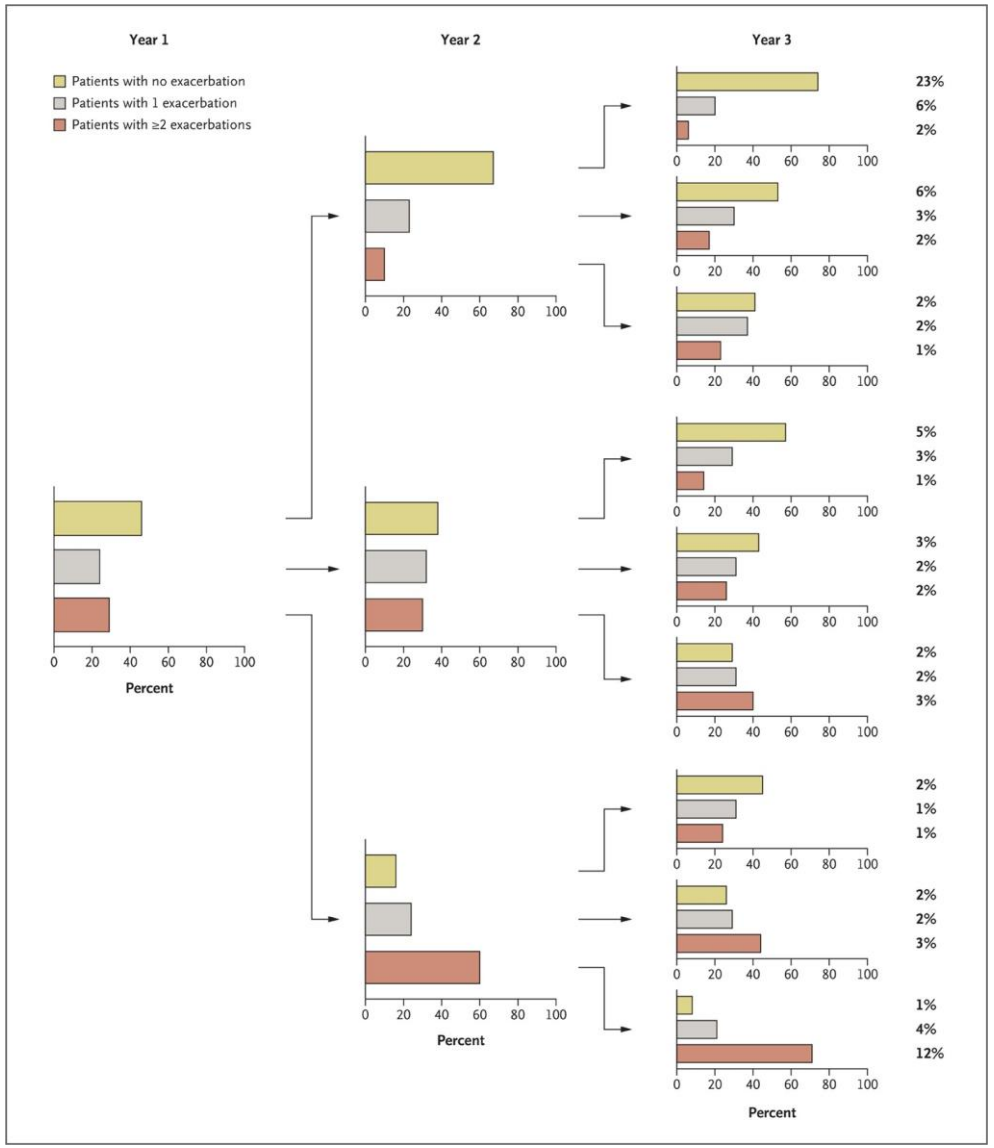
Natural course of COPD



Adapted with permission from Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645–1648

Variable prognosis in COPD

- COPD is a heterogeneous disorder with large variations.
- Exacerbations become more frequent and more severe as COPD progress.
- But, the prognosis of COPD is highly variable between patients.



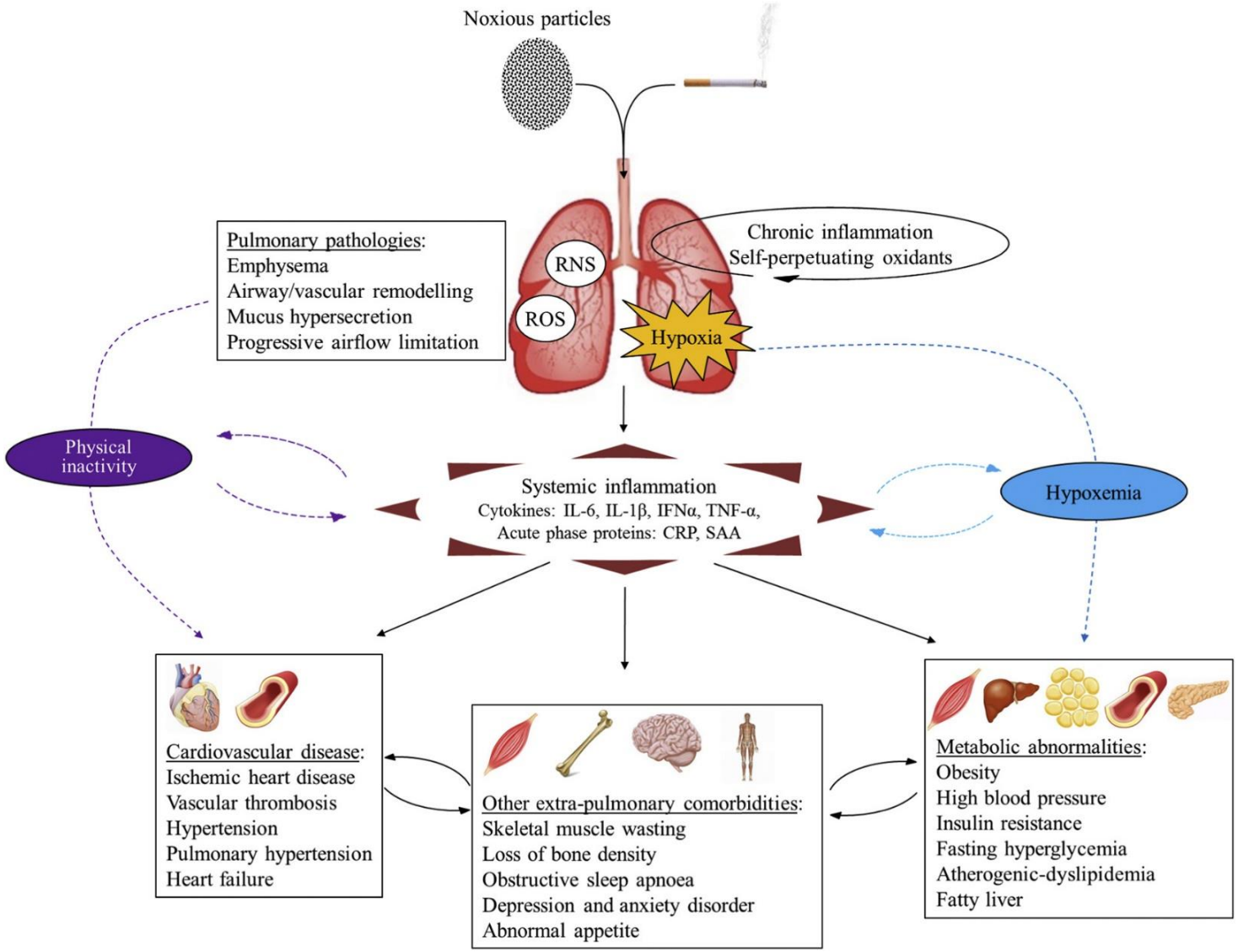
16% : no AE → any AE

5% : no AE → frequent AE

5% : frequent AE → no AE

Hurst JR et al. N Eng J Med. 2010; 363(12):1128-38

COPD is more than just a lung disorder



Chan et al. Pharmacol Ther. 2019;198:160-188.

Content

- Introduction

- **Pulmonary outcomes**
  - ✓ Exacerbation
  - ✓ Lung function
  - ✓ Pneumonia
  - ✓ Lung cancer

- Extrapulmonary outcomes
- Mortality : COPD related, all cause
- Prediction of prognosis

Goals for COPD management

Goals for treatment of stable COPD

- ✓ Relieve symptoms
- ✓ Improve exercise tolerance
- ✓ Improve health status

Reduce symptoms

And

- ✓ Prevent disease progression
- ✓ Prevent and treat exacerbation
- ✓ Reduce mortality

Reduce risk

Risk of exacerbation

2138 in ECLIPSE study

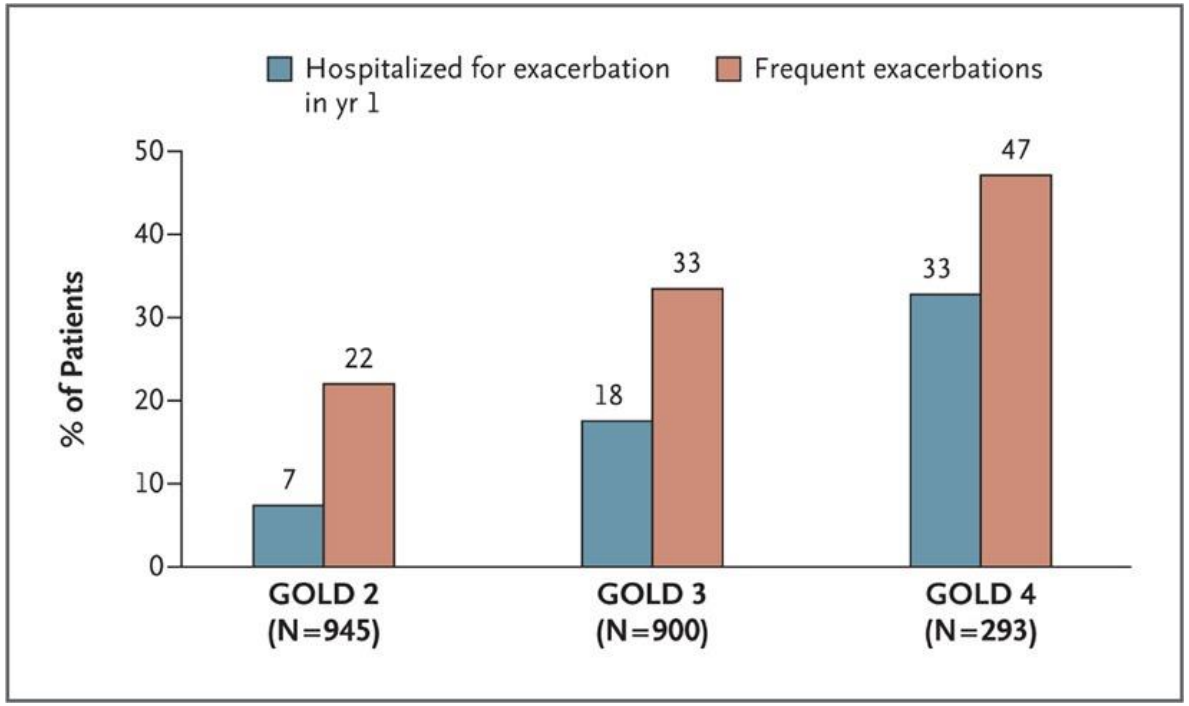


Table 3. Factors Associated with Increased Exacerbation Frequency in the Stepwise Multivariate Model.*

Factor	Number of Exacerbations						P Value for Overall Model
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Exacerbation during previous yr — any vs. none	5.72 (4.47–7.31)	<0.001	2.24 (1.77–2.84)	<0.001	2.55 (1.96–3.31)	<0.001	<0.001
FEV_1 — per 100-ml decrease	1.11 (1.08–1.14)	<0.001	1.06 (1.03–1.08)	<0.001	1.05 (1.02–1.09)	<0.001	<0.001
SGRQ score for COPD — per increase of 4 points	1.07 (1.04–1.10)	<0.001	1.01 (0.99–1.04)	0.38	1.06 (1.03–1.09)	<0.001	<0.001
History of reflux or heartburn — yes vs. no	2.07 (1.58–2.72)	<0.001	1.61 (1.23–2.10)	<0.001	1.29 (0.97–1.70)	<0.005	<0.001
White-cell count — per increase of $1\times10^3/mm^3$	1.08 (1.03–1.14)	0.002	1.02 (0.97–1.08)	0.45	1.06 (1.01–1.12)	<0.001	0.007

Exacerbation rates in the first year, per person		
0.85	1.34	2.00

- **Previous exacerbation** is the single best predictor of exacerbations, across all GOLD stages

Hurst JR. N Eng J Med. 2010; 363(12):1128-38

Exacerbation and lung function loss

- COPDGene
- change in lung function over 5 years
- Exacerbation event data collected at 6 month intervals

Table 3. Effect of Each Exacerbation/Acute Respiratory Event on Rate of FEV_1 Decline

Subject Group	Change in FEV_1 (*ml/yr*) (95% CI)			
	Exacerbations/Acute Respiratory Events of Any Severity		Severe Exacerbations/Acute Respiratory Events	
	Change in Those with No Exacerbations	Excess Change, per Exacerbation of Any Severity	Change in Those with No Severe Exacerbations	Excess Change, per Severe Exacerbation
PRISm	5 (−4 to 14)	−6 (−15 to 4)	5 (−4 to 14)	−17 (−37 to 2)
GOLD 0	−9 (−13 to −4)	−7 (−15 to 2)	−9 (−14 to −5)	−7 (−27 to 13)
GOLD 1	−25 (−34 to −15)	−23 (−44 to −2)	−26 (−35 to −16)	−87 (−151 to −23)
GOLD 2	−19 (−26 to −11)	−10 (−20 to −1)	−21 (−28 to −14)	−20 (−40 to 1)
GOLD 3	−8 (−17 to 0)	−8 (−15 to −1)	−10 (−18 to −3)	−20 (−36 to −4)
GOLD 4	−4 (−16 to 8)	0 (−9 to 8)	−2 (−13 to 8)	−9 (−29 to 12)

- ➢ Exacerbations are associated with accelerated lung function loss in COPD, particularly those with mild disease
- ➢ No significant FEV1 decline in GOLD stage 4 : possible survivor bias

Dransfield MT, et al. Am J Respir Crit Care Med. 2017;195(3):324-330.

Effect of exacerbation on survival

- Meta-analysis based on 6 studies

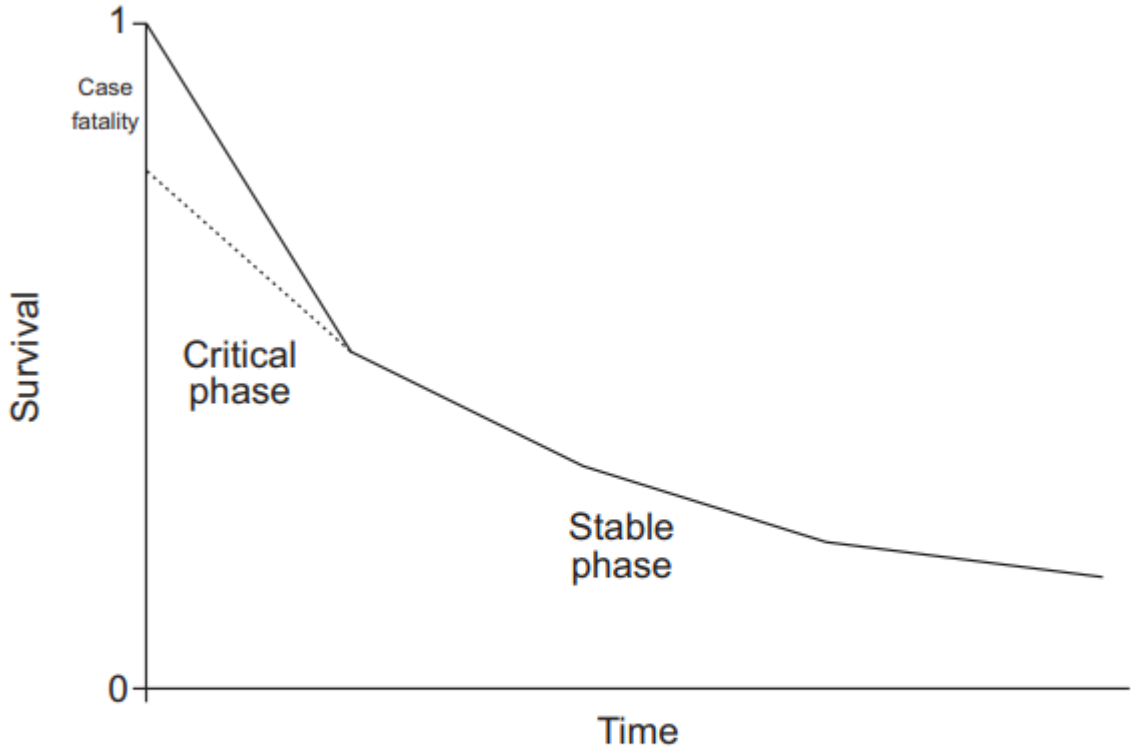


FIGURE 1. Survival curve after hospitalisation for an exacerbation of chronic obstructive pulmonary disease. ·····: the extrapolated curve during the stable phase.

- Case-fatality rate of 15.6%, ranging from 11.4% to 19% for the individual studies.
- Severe COPD exacerbation not only results in higher mortality risks during hospitalization, but also in the time-period after discharge and contributes substantially to total COPD mortality.

M. Hoogendoorn et al. Eur Respir J 2011;37(3):508-15.

Exacerbation increase the risk of further exacerbation

- 1st hospitalization for COPD during 1990-2005 (n=73,106), followed until 31 March 2007
- All COPD hospitalization occurring during follow-up were identified.

- 50,580 died during the 17-year follow-up
  - ✓ 50% mortality at 3.6 years
  - ✓ 75% mortality at 7.7 years

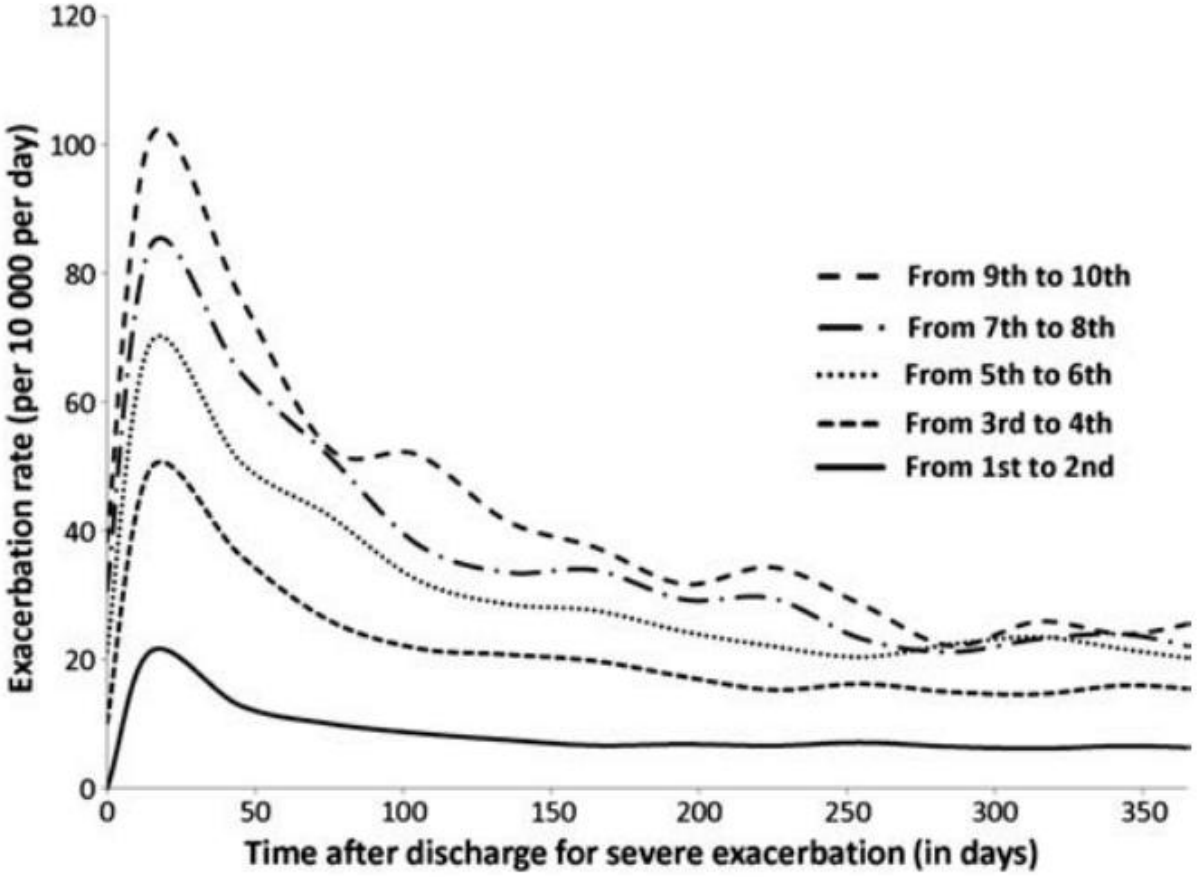
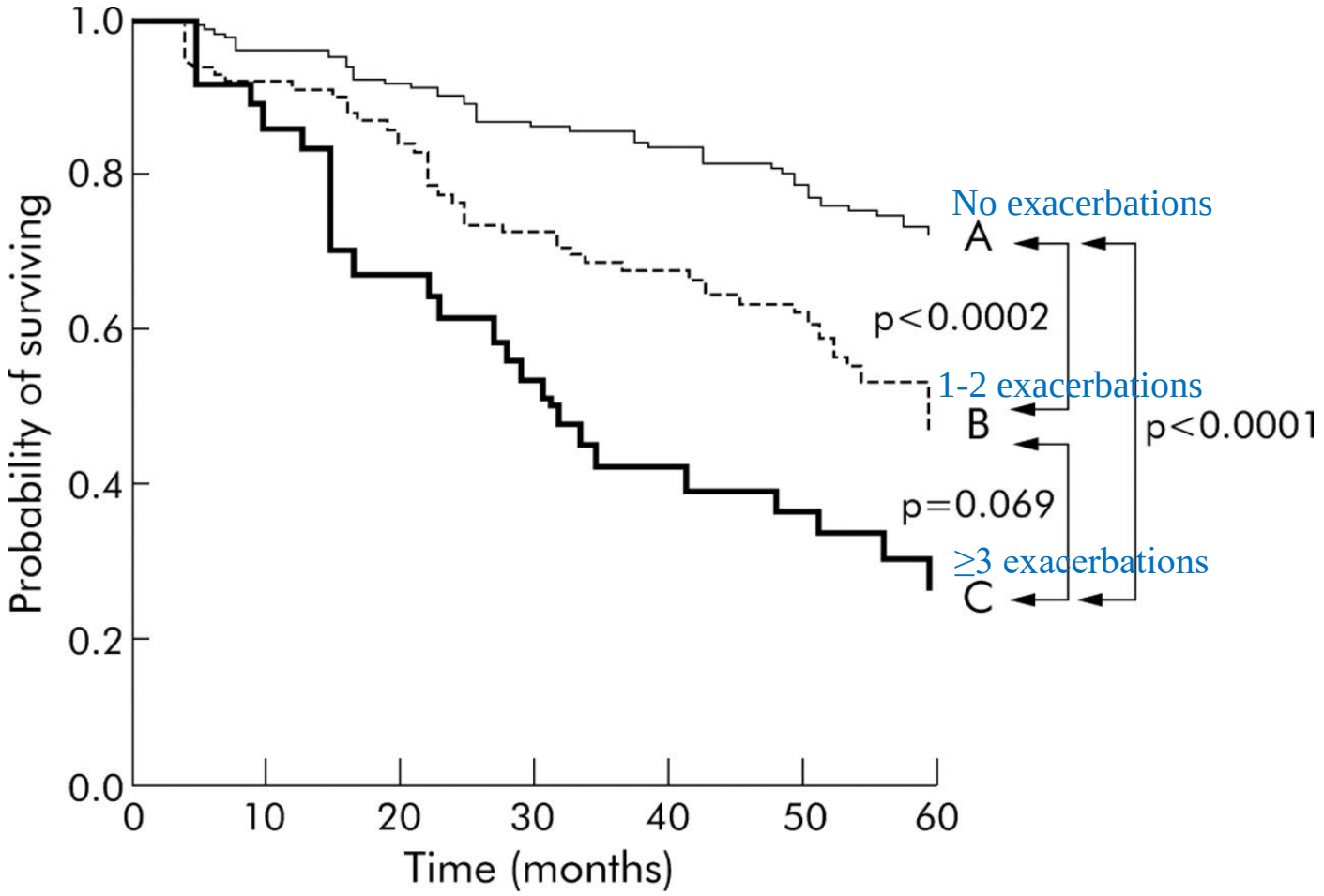


Figure 4 Hazard function of a subsequent hospitalised chronic obstructive pulmonary disease exacerbation (per 10 000 per day) in the 1-year period after discharge from the previous one.

Suissa S et al. Thorax. 2012;67(11):957-63.

Frequent exacerbation & increased mortality



- Older age, HR 5.27, 95% CI, 1.75-15.93
- PaCO2, HR 1.07, 95% CI, 1.02-1.12
- **Exacerbation**

  1-2 events : HR 2.20, 95% CI 1.45 -3.33

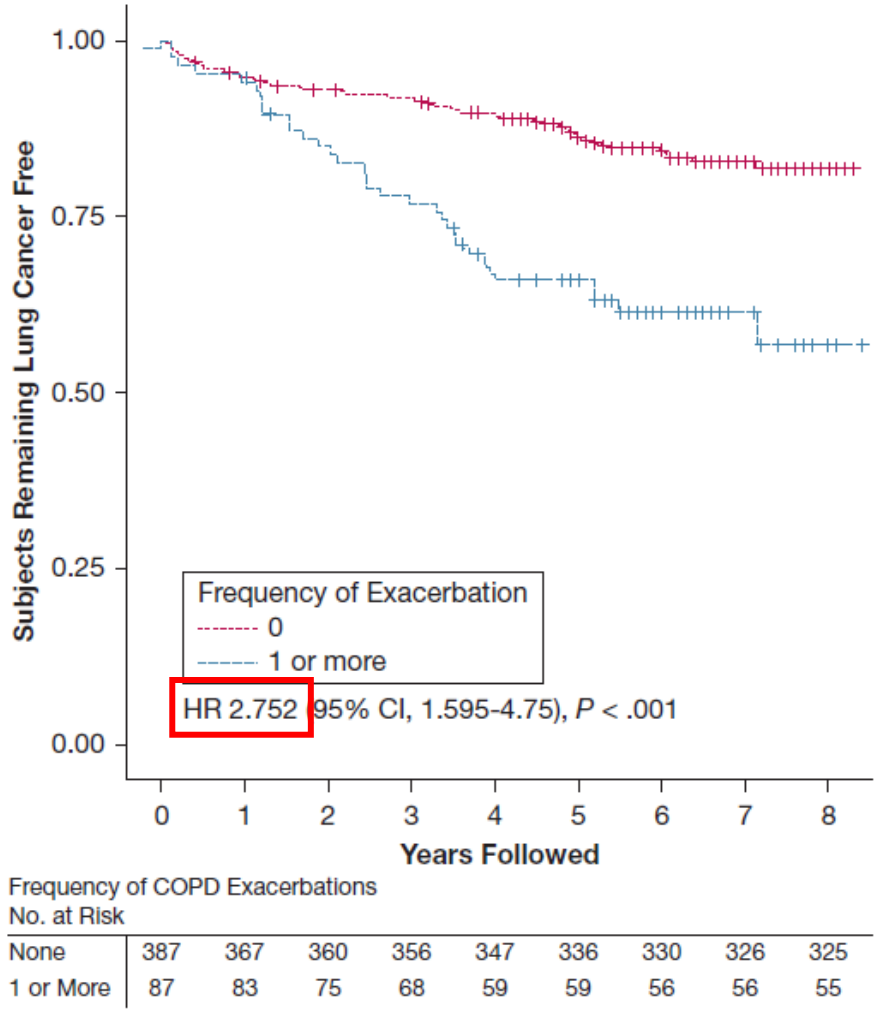
  ≥3 events : HR 4.30, 95% 2.62-7.02

J J Soler-Cataluña et al. Thorax 2005;60:925-931

Impact of exacerbation on lung cancer

- COPDGene study
- 169 subjects diagnosed with lung cancer
- average follow-up of 5.7 years
- NSCLC (n=98, adenoca (62%) > SqCC (17%)), SCLC (n=18)

- Association between SCLC histology and exacerbation
  - Exacerbation : OR 3.57 (95% CI 1.47 – 10)
  - Frequent exacerbations : OR, 4.0 (95% CI 1.58 - 10.75)



Carr LL, et al. CHEST 2018; 153(6):1326-1335

Effect of exacerbation on health care utilization

- Data from US national health plan during Jan 1, 2007 to Dec 31, 2012, aged 40-89 years, N=52,459 patients
- 26.3% had one, 9.5% had two, and 8.5% had ≥three exacerbations in the 24-month follow-up period

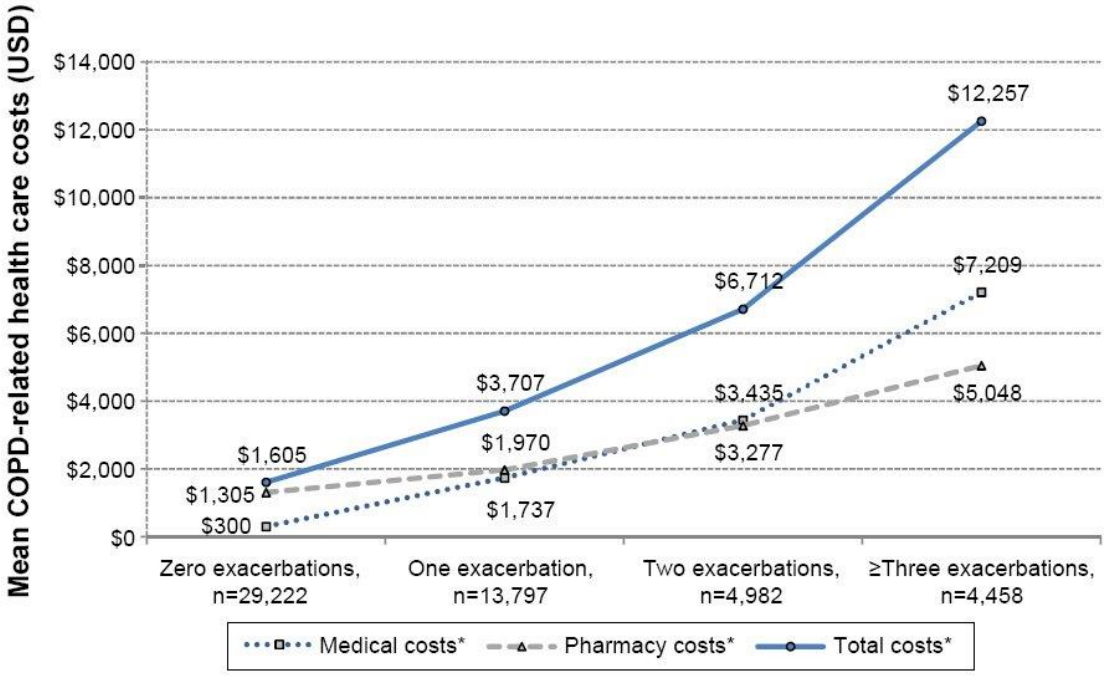


Figure 2 COPD-related health care costs by exacerbation frequency.
Note: *Statistically significant ($P<0.001$) trend.
Abbreviation: USD, United States dollar.

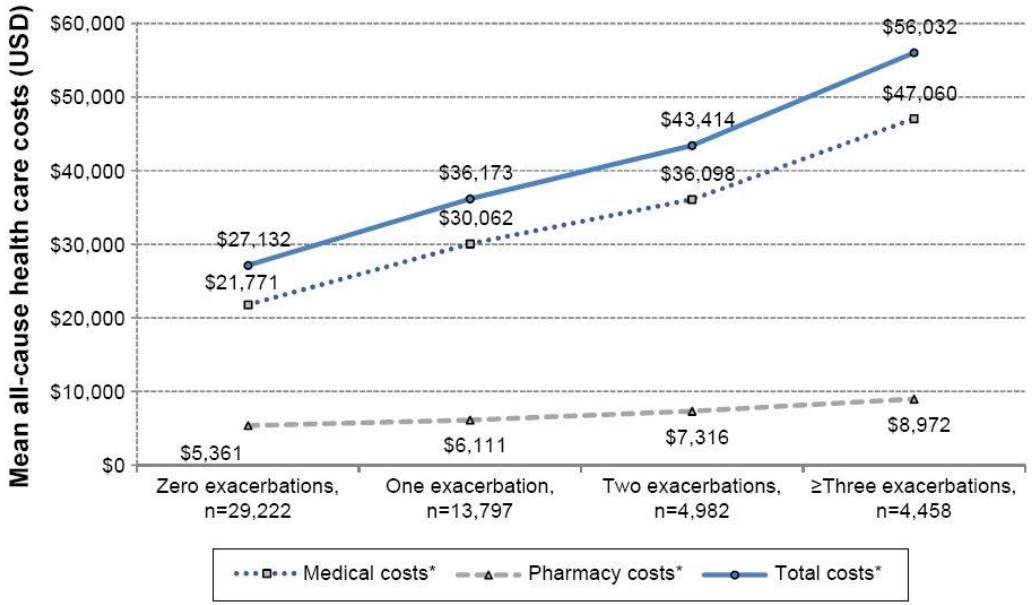


Figure 3 All-cause health care costs by exacerbation frequency.
Note: *Statistically significant ($P<001$) trend.
Abbreviation: USD, United States dollar.

Dhamane AD, et al. Int J Chron Obstruct Pulmon Dis. 2015:10 2609–2618

FEV1 decline

- Copenhagen City Heart Study : FEV1 change for 18 years

	Decline in FEV_1 in mL per year	p value	p value	p value	p value
Healthy never-smokers	20·9 (1·2)	Reference	0·15	<0·0001	0·19
Ever-smokers without asthma or COPD	20·7 (1·4)	0·88	0·13	<0·0001	0·17
Asthma	25·6 (3·3)	0·15	Reference	0·0003	0·77
COPD	39·5 (2·5)	<0·0001	0·0003	Reference	0·02
ACO with early asthma onset	27·3 (5·0)	0·19	0·77	0·02	Reference
ACO with late asthma onset	49·6 (3·0)	<0·0001	<0·0001	0·003	0·0001
Male sex (reference: female sex)	4·8 (1·2)	<0·0001	..	..	..
Age (years)	0·6 (0·1)	<0·0001	..	..	..
Height (cm)	0·4 (0·1)	<0·0001	..	..	..
Smoking (reference: non-smokers)					
Quitters	2·3 (1·8)	0·22	..	..	..
Current smokers	8·0 (1·1)	<0·0001	..	..	..
BMI (kg/m^2; reference: changes of <3 kg/m^2)					
Decrease >3 kg/m^2	−10·8 (2·7)	0·0001	..	..	..
Increase >3 kg/m^2	11·3 (1·5)	<0·0001	..	..	..

Table 3: **Decline in FEV_1 according to different types of airway disease**

- 6 subgroups (n=8382)
  - healthy never-smoker (n=2199)
  - ever-smoker (n=5435)
  - asthma with low smoking exposure & no AFL (n=158)
  - COPD (n=320)
  - ACO with early onset asthma (n=68)
  - ACO with late-onset asthma (n=202)

- Multivariable-adjusted decline in FEV1 in COPD is much faster than healthy, asthma, ACO with early asthma onset

Lange P et al. Lancet Respir Med 2016; 4: 454–62

FEV1 decline & exacerbation risk

- 2,138 COPD patients in ECLIPSE cohort
- 670 (31%) had a total of 1,452 severe COPD exacerbations

TABLE 2] Baseline Risk Factors of Hospitalized Exacerbation During Follow-up

Parameter[a]	HR	HR (95% CI)	*P* Value
COPD hospitalization, prior 12 mo	2.71	(2.24, 3.29)	<.001
SGRQ total score, per 4-point increase	1.08	(1.06, 1.10)	<.001
FEV_1 % predicted, per 5% drop	1.12	(1.09, 1.16)	<.001
Age, per 10-y increment	1.29	(1.13, 1.46)	<.001
Has emphysema, >5% by radiology	1.56	(1.23, 1.97)	<.001
WBC count, per 1×10^9/L	1.15	(1.07, 1.24)	<.001

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.
[a]Model was also adjusted for sex and smoking status at baseline (both nonsignificant). Ordered by strength of association.

TABLE 3] Baseline Risk Factors of Hospitalized Exacerbation in Patients With COPD Without a History of Hospitalized Exacerbation 12 Mo Prior to the Study

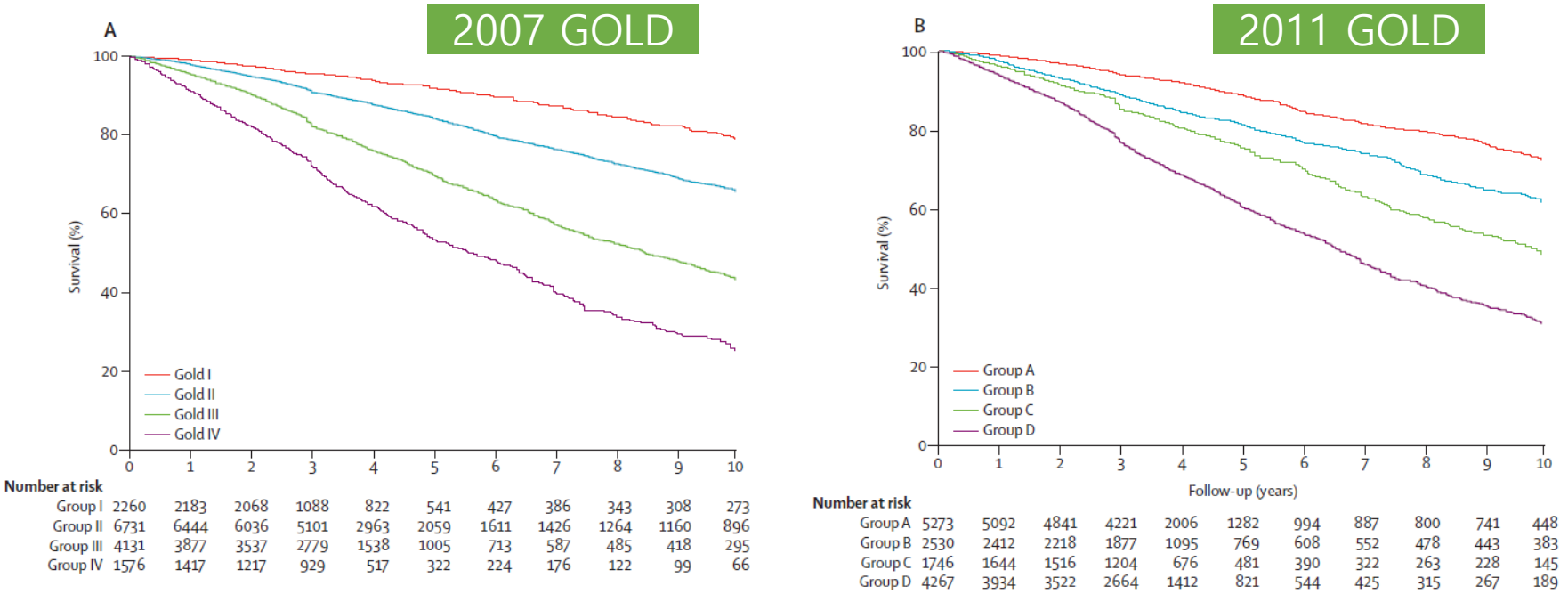
Parameter[a]	HR	HR (95% CI)	*P* Value
SGRQ total score, per 4-point increase	1.08	(1.05, 1.11)	<.001
FEV_1 % predicted, per 5% drop	1.11	(1.07, 1.15)	<.001
Has emphysema, >5% by radiology	1.71	(1.28, 2.26)	<.001
Oxygen use at baseline	1.75	(1.30, 2.35)	<.001
History of asthma	1.45	(1.17, 1.79)	<.001
Age, per 10-y increment	1.24	(1.07, 1.44)	.005
Fibrinogen, per 1 log SD	1.15	(1.04, 1.28)	.008

See Table 1 and 2 legends for expansion of abbreviations.
[a]Model was also adjusted for sex and smoking status at baseline (both nonsignificant). Ordered by strength of association.

Mullerova H, et al. Chest. 2015;147(4):999-1007.

Severity of AFL & mortality

- 15,632 patients from 22 COPD cohorts, mortality within 10 years



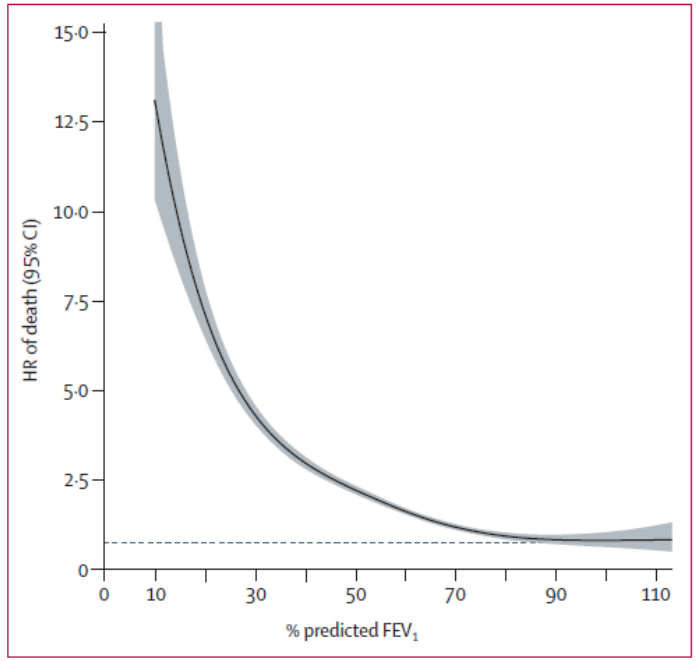


Figure 4: Spline of the HR of death to identify spirometry thresholds of severity n=15 632. 100% predicted FEV_1 is taken as the reference point (hazard ratio [HR]=1). FEV_1=forced expiratory volume in 1 s.

✓ However, FEV1 by itself lacks sufficient precision to be used clinically as a predictor of exacerbation or mortality in patients with COPD

Soriano JB, et al. Lancet Respir Med. 2015;3(6):443-50.

Pneumonia in COPD

- Risk of CAP is higher in COPD patients than in the general population, particularly in aged over 65 years with severe COPD
  - 8% (3,149 of 40,414 COPD patients) experienced pneumonia, IR 22.4 per 1000 person years
  - OR for CAP occurrence 1.28 and 1.86 in patients aged over 65 and 80 years

Mullerova H et al. Respir Med 2012; 106(8):1124-1133.

- 19% of CAP patients had COPD & 10% of CAP patients led to the new diagnosis of COPD
  - longer hospital stay, increased ICU admission, and mortality

Pifarre et al. Respir Med. 2007;101(10):2139-44.

Risk of hospital admission

Copenhagen City Heart Study : hospital admission for exacerbation or pneumonia for 22 years

	Participants (n)	Acute hospital admission for COPD and asthma			Acute hospital admission for pneumonia		
		Events (n [%])	Hazard ratio (95% CI)*	p value	Events (n [%])	Hazard ratio (95% CI)*	p value
Adjusted for age and sex	**8382**	**929 (15%)**			**1687 (27%)**		
Never-smokers without disease	2199	62 (4%)	1·00 (reference)		333 (19%)	1·00 (reference)	
Ever-smokers without disease	5435	511 (14%)	3·93 (3·02–5·13)	<0·0001	1076 (27%)	1·50 (1·32–1·69)	<0·0001
Asthma	158	46 (35%)	14·74 (10·06–21·59)	<0·0001	33 (25%)	2·00 (1·40–2·86)	0·0002
COPD	320	123 (70%)	23·80 (17·43–32·50)	<0·0001	127 (70%)	3·67 (2·98–4·53)	<0·0001
ACO with early asthma onset	68	34 (58%)	39·48 (25·93–60·11)	<0·0001	22 (49%)	3·56 (2·31–5·49)	<0·0001
ACO with late asthma onset	202	153 (94%)	83·47 (61·67–112·98)	<0·0001	96 (81%)	6·39 (5·07–8·05)	<0·0001
Adjusted for age, sex, BMI, and FEV_1 % of predicted value	**8367**	**922 (15%)**			**1684 (27%)**		
Never-smokers without disease	2199	62 (4%)	1·00 (reference)		333 (19%)	1·00 (reference)	
Ever-smokers without disease	5435	511 (14%)	3·40 (2·61–4·43)	<0·0001	1076 (27%)	1·37 (1·21–1·56)	<0·0001
Asthma	143	39 (32%)	8·29 (5·52–12·44)	<0·0001	30 (24%)	1·54 (1·06–2·25)	0·02
COPD	320	123 (70%)	7·75 (5·56–10·82)	<0·0001	127 (70%)	1·94 (1·54–2·44)	<0·0001
ACO with early asthma onset	68	34 (58%)	9·00 (5·75–14·10)	<0·0001	22 (49%)	1·58 (1·01–2·48)	0·04
ACO with late asthma onset	202	153 (94%)	14·74 (10·40–20·91)	<0·0001	96 (81%)	2·43 (1·86–3·18)	<0·0001
Adjusted for age, sex, BMI, and pack-years	**581**	**306 (75%)**			**243 (70%)**		
COPD	320	123 (70%)	1·00 (reference)		127 (70%)	1·00 (reference)	
ACO with early asthma onset	67	34 (59%)	1·90 (1·26–2·87)	0·002	22 (50%)	1·27 (0·79–2·06)	0·32
ACO with late asthma onset	194	149 (94%)	3·52 (2·74–4·54)	<0·0001	94 (82%)	1·78 (1·34–2·36)	<0·0001

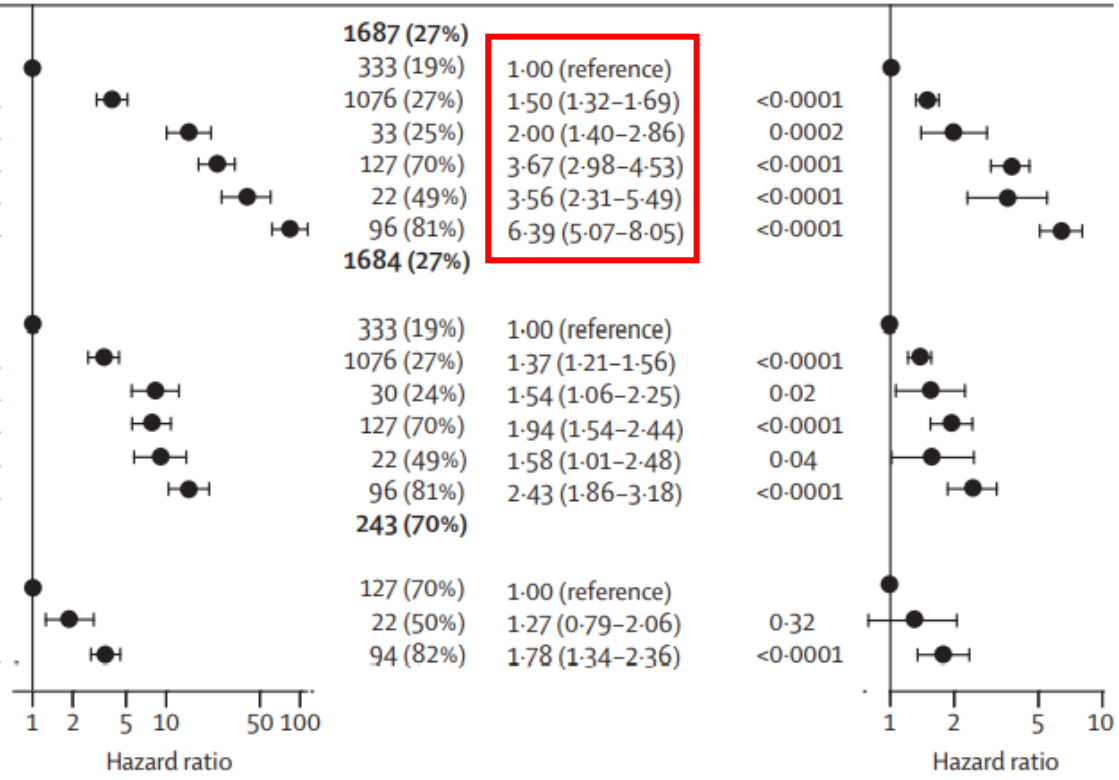


***Figure 3*: Risk of acute hospital admissions due to COPD and asthma and due to pneumonia in the six subgroups defined by smoking and presence of airway disease**
The x-axis is a log scale. Percentages are Kaplan-Meier estimates. COPD=chronic obstructive pulmonary disease. ACO=asthma-COPD overlap. BMI=body-mass index. FEV_1=forced expiratory volume in 1 s. *Estimated with Cox regression.

Lange P et al. Lancet Respir Med 2016; 4: 454–62

Pathogenesis of COPD and pneumonia

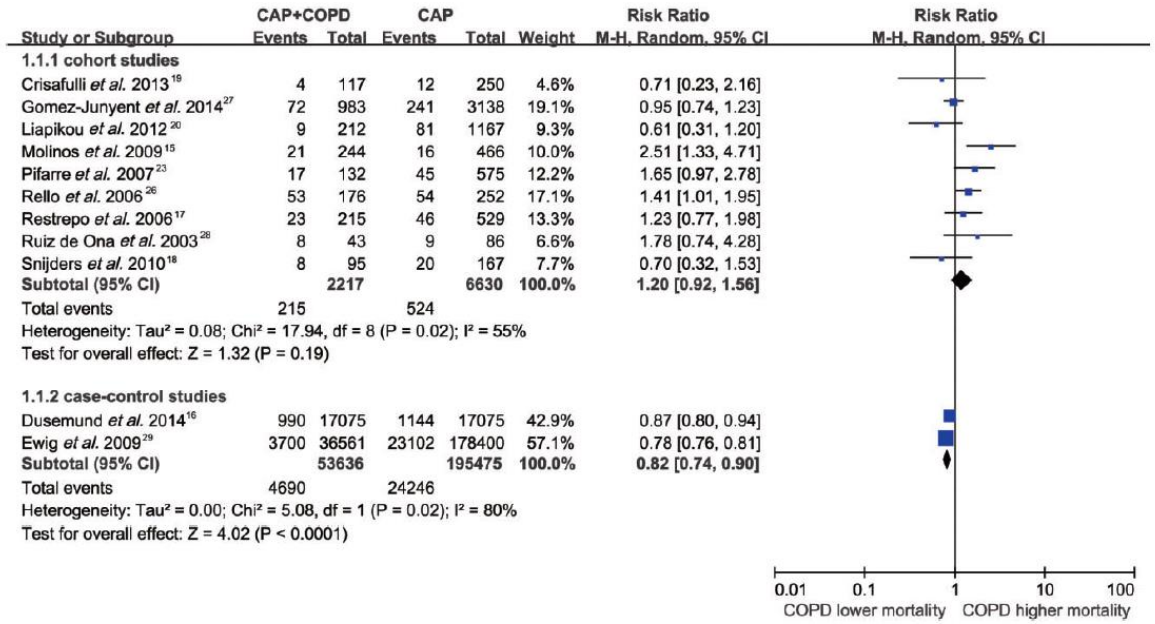
- **COPD itself**
  - ✓ impaired lung defence (e.g. reduced mucociliary clearance, disruption of epithelial barrier and reduced repair)
  - ✓ inflammation : mediators involved in both COPD and pneumonia such as IL-1, IL-6, IL-8, MMP-8, MMP-9
  - ✓ Immune system : activated CD8+ cytotoxic T cells
  - ✓ increased tracheobronchial microbial colonization
  - ✓ *α*1-antitrypsin deficiency
- **Shared risk factors** : age, smoking
- **ICS use**
  - ✓ Suppression of the cellular and humoral arms of immunity (e.g. decreased phagocytosis and production of NO by alveolar macrophages)

Gautam SS et al. COPD. 2016;13(6):790-798.

Is COPD associated with increased risk of pneumonia & morbidity/mortality ?

Con

Meta-analysis of 11 studies involving 257,958 patients



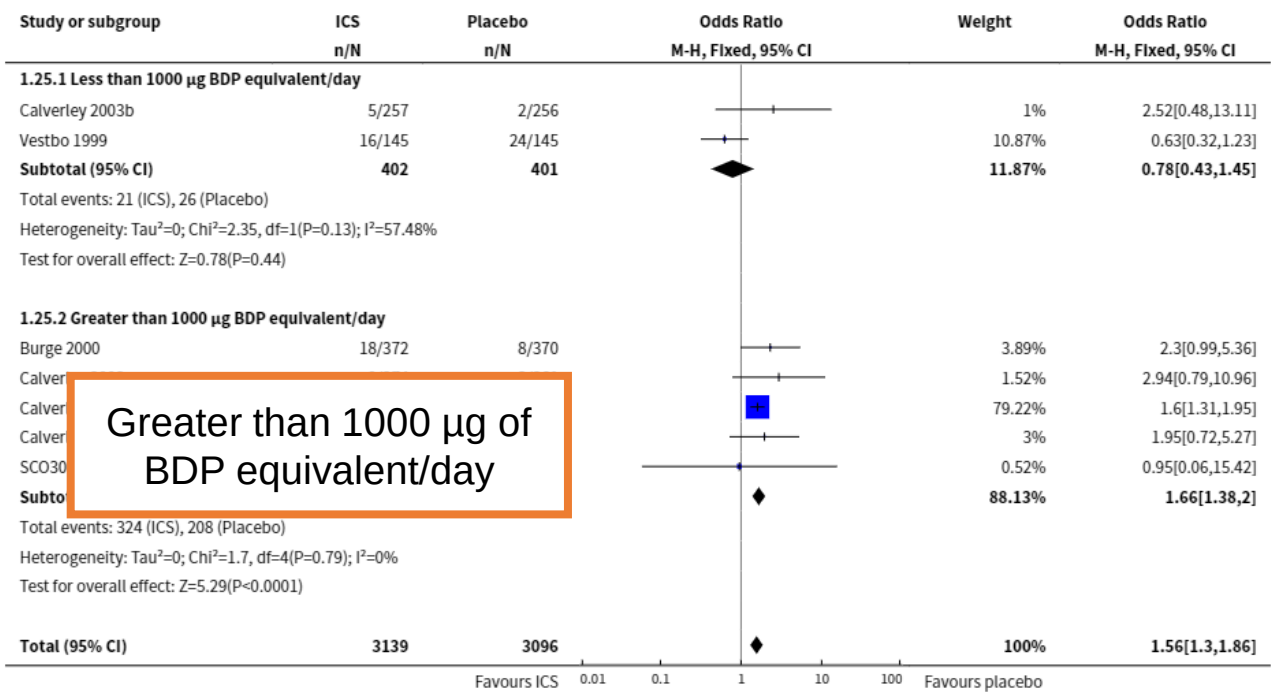
Study or Subgroup	CAP+COPD Events	Total	CAP Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 cohort studies						
Crisafulli *et al.* 2013 [19]	4	117	12	250	4.6%	0.71 [0.23, 2.16]
Gomez-Junyent *et al.* 2014 [27]	72	983	241	3138	19.1%	0.95 [0.74, 1.23]
Liapikou *et al.* 2012 [20]	9	212	81	1167	9.3%	0.61 [0.31, 1.20]
Molinos *et al.* 2009 [15]	21	244	16	466	10.0%	2.51 [1.33, 4.71]
Pifarre *et al.* 2007 [23]	17	132	45	575	12.2%	1.65 [0.97, 2.78]
Rello *et al.* 2006 [26]	53	176	54	252	17.1%	1.41 [1.01, 1.95]
Restrepo *et al.* 2006 [17]	23	215	46	529	13.3%	1.23 [0.77, 1.98]
Ruiz de Ona *et al.* 2003 [28]	8	43	9	86	6.6%	1.78 [0.74, 4.28]
Snijders *et al.* 2010 [18]	8	95	20	167	7.7%	0.70 [0.32, 1.53]
Subtotal (95% CI)		**2217**		**6630**	**100.0%**	**1.20 [0.92, 1.56]**
Total events	215		524			
Heterogeneity: Tau² = 0.08; Chi² = 17.94, df = 8 (P = 0.02); I² = 55%						
Test for overall effect: Z = 1.32 (P = 0.19)						
1.1.2 case-control studies						
Dusemund *et al.* 2014 [16]	990	17075	1144	17075	42.9%	0.87 [0.80, 0.94]
Ewig *et al.* 2009 [29]	3700	36561	23102	178400	57.1%	0.78 [0.76, 0.81]
Subtotal (95% CI)		**53636**		**195475**	**100.0%**	**0.82 [0.74, 0.90]**
Total events	4690		24246			
Heterogeneity: Tau² = 0.00; Chi² = 5.08, df = 1 (P = 0.02); I² = 80%						
Test for overall effect: Z = 4.02 (P < 0.0001)						

Figure 2 Forest plot for mortality in patients with CAP + COPD and CAP only in cohort studies and case–control studies. (■) The risk ratio for each study, (——) confidence interval, (◆) pooled result for all cohort studies and case–control studies. CAP, community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; df, degrees of freedom; M-H, Mantel–Haenszel method.

Jiang HL et al. Respirology (2015) 20, 1046–1054

Pro

Meta-analysis of 55 studies involving 16,154 patients



Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.25.1 Less than 1000 µg BDP equivalent/day					
Calverley 2003b	5/257	2/256		1%	2.52[0.48,13.11]
Vestbo 1999	16/145	24/145		10.87%	0.63[0.32,1.23]
Subtotal (95% CI)	**402**	**401**		**11.87%**	**0.78[0.43,1.45]**
Total events: 21 (ICS), 26 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.35, df=1(P=0.13); I²=57.48%					
Test for overall effect: Z=0.78(P=0.44)					
1.25.2 Greater than 1000 µg BDP equivalent/day					
Burge 2000	18/372	8/370		3.89%	2.3[0.99,5.36]
Calver				1.52%	2.94[0.79,10.96]
Calver				79.22%	1.6[1.31,1.95]
Calver				3%	1.95[0.72,5.27]
SCO30				0.52%	0.95[0.06,15.42]
Subto				**88.13%**	**1.66[1.38,2]**
Total events: 324 (ICS), 208 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.7, df=4(P=0.79); I²=0%					
Test for overall effect: Z=5.29(P<0.0001)					
Total (95% CI)	**3139**	**3096**		**100%**	**1.56[1.3,1.86]**

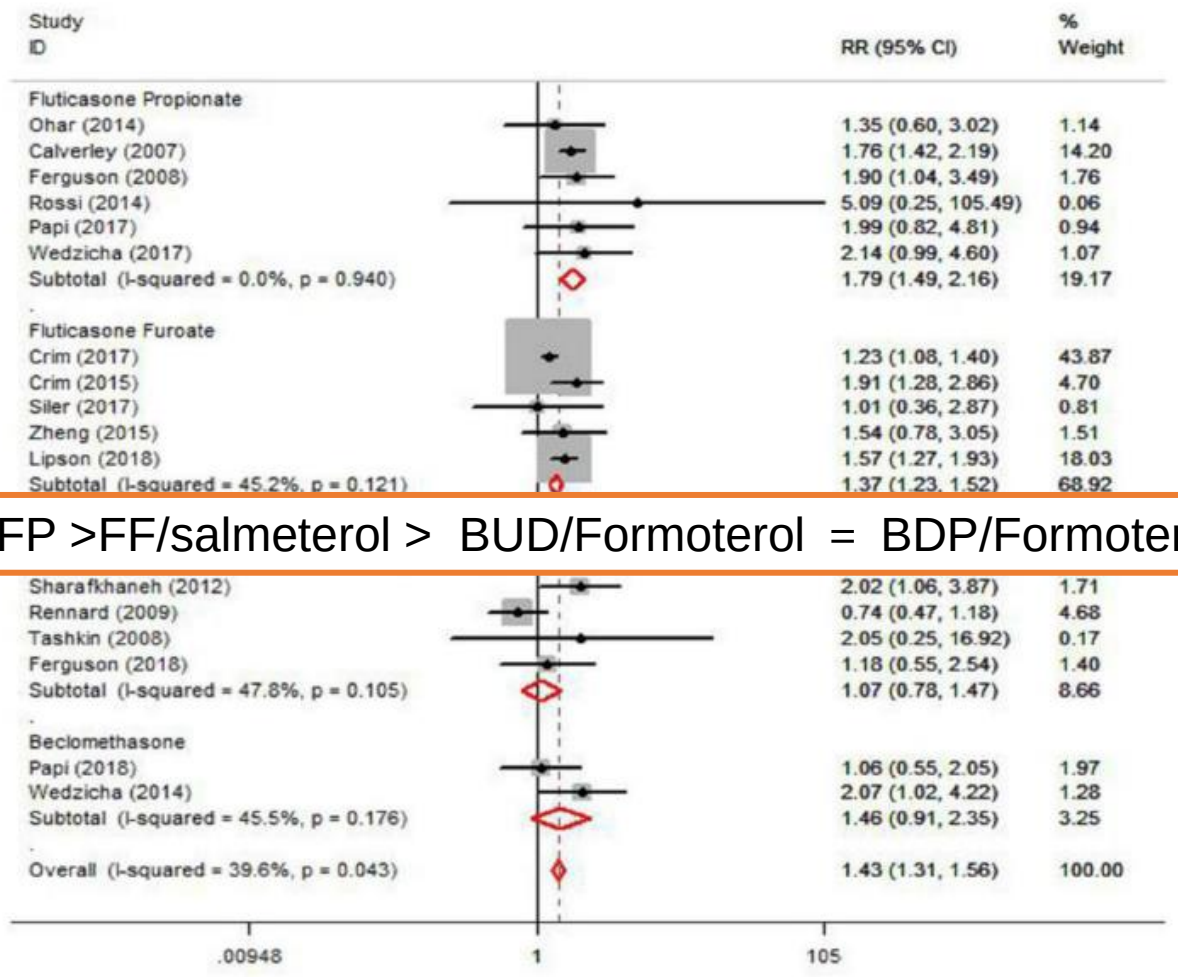
Greater than 1000 µg of BDP equivalent/day

- intra-class difference
- dosage

Yang IA. Cochrane Database Syst Rev. 2012;(7):CD002991.

Risk of pneumonia with different ICS

Meta-analysis of 18 RCTs (n=49,828)



FP >FF/salmeterol > BUD/Formoterol = BDP/Formoterol

Figure 5. Subgroup analysis of the risk of pneumonia with the use of different types of ICS.

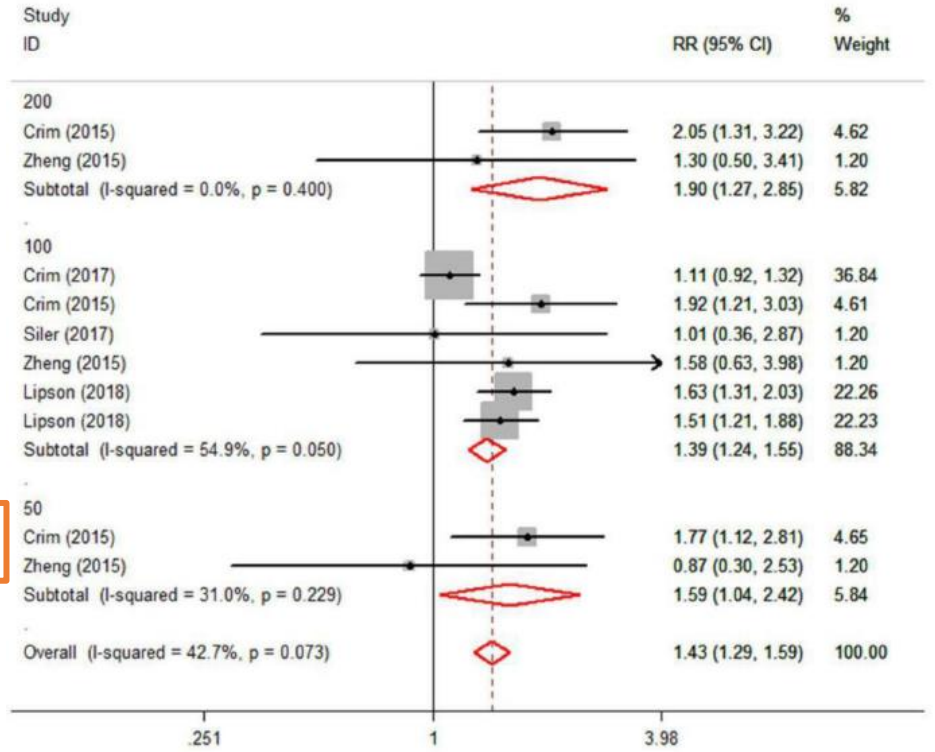
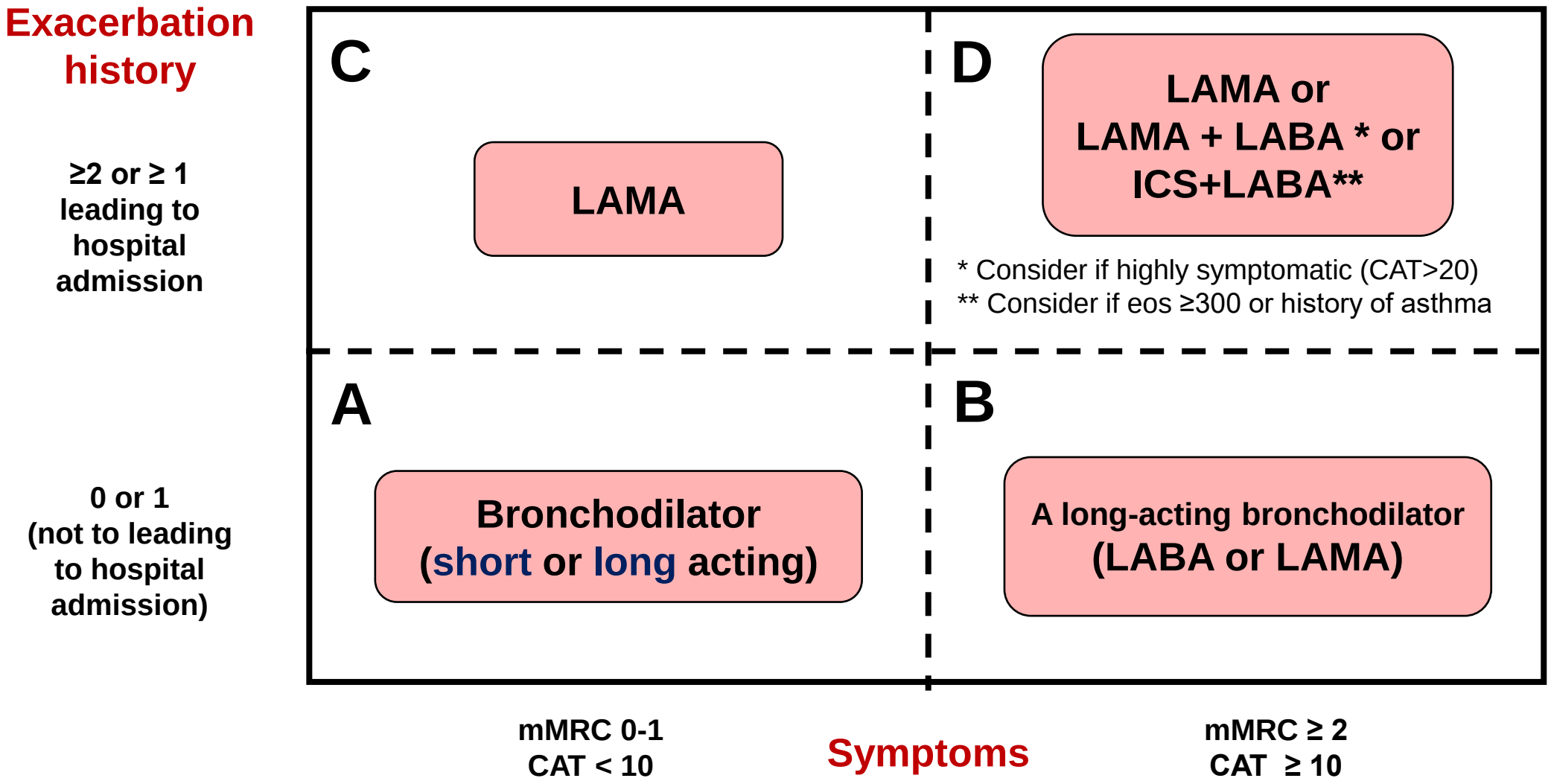


Figure 7. Subgroup analysis of the risk of pneumonia between high, medium and low dose of fluticasone furoate.

Zhagn et al. COPD. 2020;17(4):462-469.

Initial pharmacological treatment



Pneumonia risk : Triple vs ICS/LABA vs LABA/LAMA

IMPACT trial

- **Inclusion** : age≥40, CAT ≥10 and either
  - FEV_1<50% pred & ≥ 1 mod or sev AE
  - FEV_1 50-80% pred & ≥2 mod or ≥1 sev AE
  - ► Mean CAT score: 20.1± 6.1
- Single Ellipta inhaler, DPI, 52wks, N=10,355
- FF/VI/UMEC 100/25/62.5 µg vs FF/VI vs VI/UMEC (n=4151 vs 4134 vs 2070)
- Primary endpoint: moderate to severe AE

Table 3. Adverse Events of Special Interest in the Intention-to-Treat Population.*

Event	Triple Therapy (N=4151)		Fluticasone Furoate–Vilanterol (N=4134)		Umeclidinium–Vilanterol (N=2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)

ARI 2.67%
NNH 37.5

Lipson DA et al. N Engl J med 2018;378:1671-80.

Lung cancer and COPD

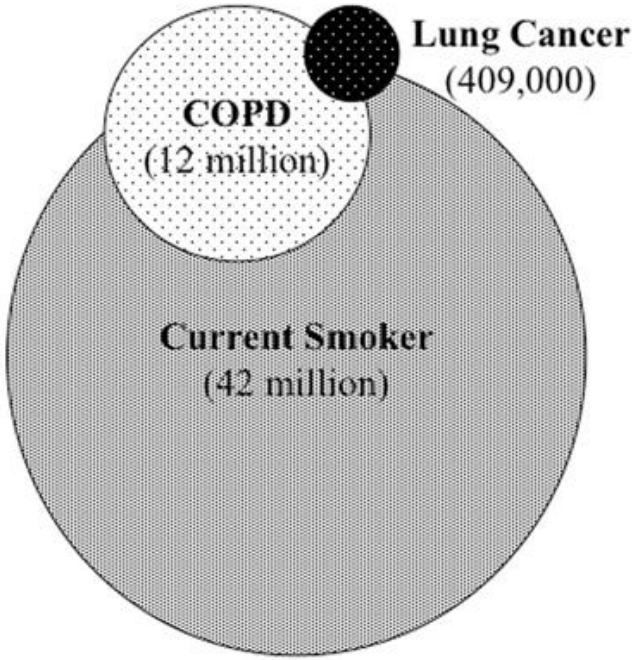
- **RR for lung cancer**

✓ Previous history of COPD : RR of 2.22 (95% CI, 1.66-2.97) from 16 studies

✓ chronic bronchitis: RR of 1.52 (95% CI, 1.25-1.84) from 23 studies

✓ Emphysema : RR of 2.04 (95% CI, 1.72-2.41) from 20 studies

➔ RR for combined disease of 1.80 (95% CI, 1.60-2.11) from 39 studies



- ICES-derived public healthcare data (2002-2014) of 105, 304 subjects diagnosed with lung cancer

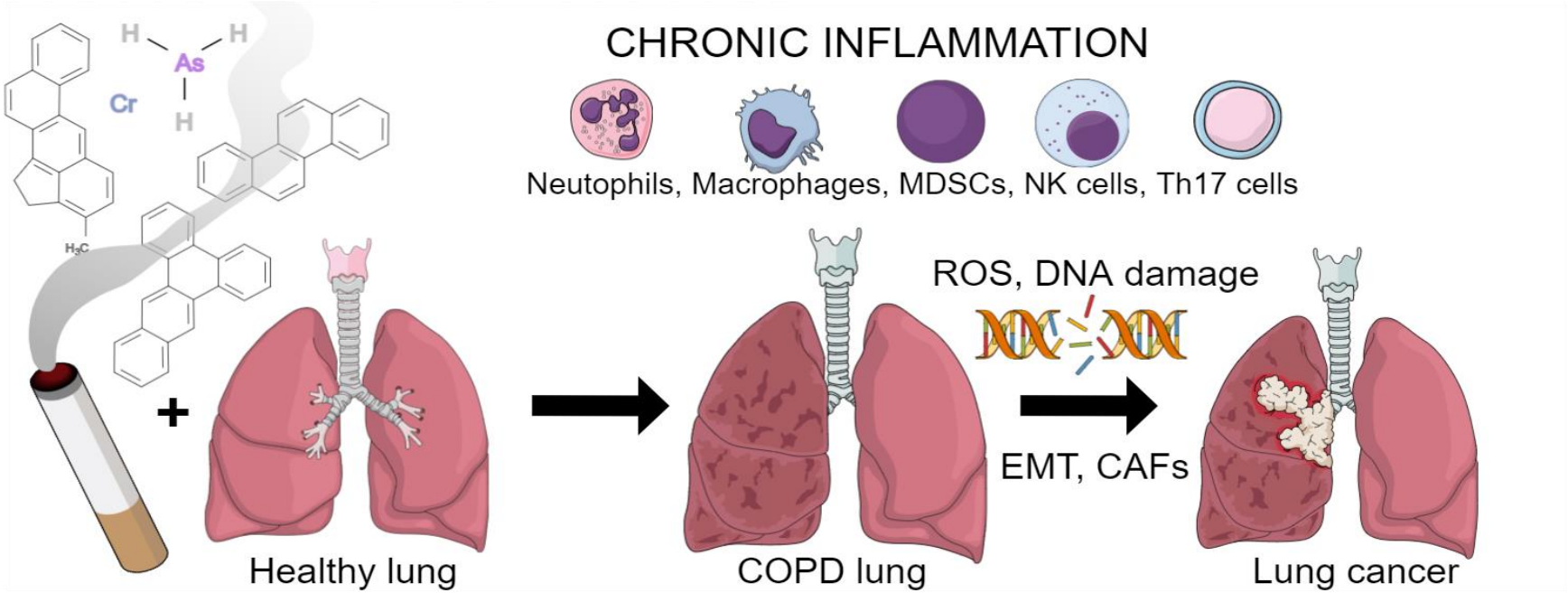
✓ Spirometry was taken in 90.6% in stage I-II vs 54.4% in stage III-IV lung cancer

✓ previous COPD diagnosed in 34.9%

➔ over 1/3 of individuals with lung cancer had a prior diagnosis of COPD.

Lambert AA, et al. Chronic Obstr Pulm Dis. 2016;3(1):459-465.
Brenner DR et al. PLoS One. 2011;6(3):e17479.
Corriveau et al. BMC Cancer (2021) 21(1):14

Pathogenetic links between COPD and lung cancer



- Genetic susceptibility
  (e.g. SERPINA, HHIP, FAM13A, CHRNA3,5)
- Epigenetic change (e.g. RASSF1A, MGMT, CDKN2A, RB1)
- Cell cycle regulation

- Chronic inflammation
- Oxidative stress
- Epithelial-mesenchymal transition (EMT)
- Telomere shortening

Szalontai K et al. J. Clin. Med. 2021, 10(13), 2889
Houghton AM. et al. Nat Rev Cancer. 2013;13(4):233-45.

Lung cancer risk

- 13,939 current-or former smokers aged from 55-74years from the National Lung Cancer Screening Trial (NLST)

Table 2. Adjusted risk of lung cancer according to study group

Characteristic	ACO	COPD	Smokers with Asthma	GOLD U	Smokers with Normal Spirometry
Number of subjects	208	4,428	281	2,547	6,447
Number of lung cancers	16	305	3	117	163
Person-years	1,208	26,083	1,706	15,214	39,625
Lung cancer rate, per 1,000 person-years	13.2 (8.1–21.5)	11.7 (10.5–13.1)	1.8 (0.6–5.4)	7.7 (6.4–9.2)	4.1 (3.5–4.8)
Unadjusted IRR (95% CI)	IRR of ACO compared with	1.14 (0.69–1.88)	7.58 (2.21–26.02)	1.72 (1.03–2.92)	3.23 (1.93–5.40)
Adjusted IRR (95% CI)*		1.21 (0.69–2.12)	5.07 (1.44–17.83)	1.63 (0.91–2.92)	2.68 (1.52–4.74)

Definition of abbreviations: ACO = asthma–COPD overlap; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GOLD-U = Global Initiative for Chronic Obstructive Lung Disease–Unclassified; IRR = incidence rate ratio.
*Adjusted for randomization group, age, sex, race/ethnicity, marital status, education, lung cancer family history, history of asbestos exposure, body mass index, current versus former smoker status, and pack-years smoked.

Charokopos AS, et al. Ann Am Thorac Soc. 2021;18(11):1894-1900.

Lung cancer incidence in never smoker COPD

- National Health Insurance Service (NHIS) Cohort, 338,548 subjects, 40-84 years of age
- Median 7 years follow-up
- 1,834 subjects developed lung cancer : 1544 in non COPD (incidence rate 0.47 per 1000 person-years), 290 in COPD (incidence rate 4.9 per 1000 person-years) ➔ aHR 3.12 (2.66-3.65)

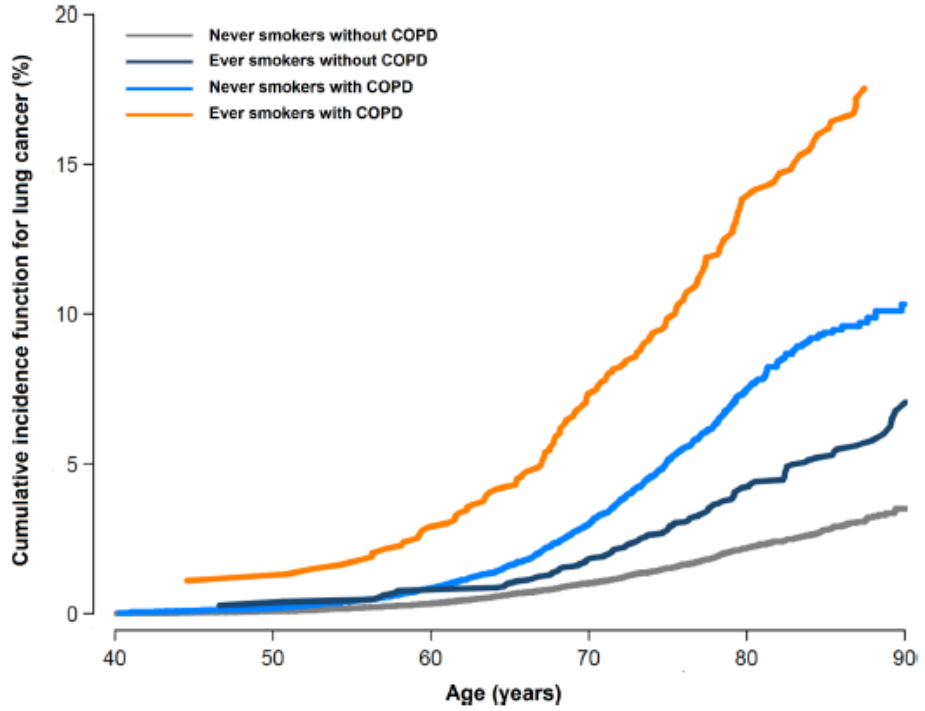


Figure 1 Cumulative incidence function for lung cancer by chronic obstructive pulmonary disease (COPD) and smoking status. COPD was considered as a time-varying exposure. Unexposed person-time was contributed by participants who did not develop COPD and by participants who developed lung cancer before COPD development. Cumulative incidence functions take into account competing risks from all-cause mortality.

Incidence for lung cancer	Incidence rate (per 1,000 person-years)	aHR (95% CI)
Never smoker, non-COPD	0.5	Reference
Never smoker, COPD	3.0	2.67 (2.09 - 3.40)
Ever smoker, non-COPD	1.2	1.97 (1.75 - 2.21)
Ever smoker, COPD	9.5	6.19 (5.04 - 7.61)

Park HY, et al. Thorax 2020;75:506–509.

Features of COPD as predictors of lung cancer

- Nested case-control study of COPDGene study
- 45-80 years of age, at least 10-pack years smoking history
- Over 8 years of follow-up
- 169 subjects diagnosed with lung cancer, average follow-up of 5.7 years

TABLE 4] Factors Associated With a Lung Cancer Diagnosis in the Multivariable Model

	Lung Cancer Diagnosis			
	Model 1		Model 2	
Factor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
FEV_1/FVC per 10% decrease	1.28 (1.12-1.46)	< .001	–	
FEV_1 ppd per 5% decrease	…		1.07 (1.03-1.12)	< .001
Exacerbations in year prior to enrollment per event increase (0, 1, and ≥ 2)	1.39 (1.04-1.85)	.02	1.37 (1.02-1.82)	.03
Visual emphysema: none-trace vs mild-advanced	2.31 (1.41-3.76)	< .001	2.64 (1.66-4.30)	< .001

Carr LL, et al. CHEST 2018; 153(6):1326-1335

Impact of COPD on lung cancer treatment and survival

- ICES-derived COPD cohort (2002 to 2014)
- In total 105,304 subjects with lung cancer, 43,375 (41%) had stage data & 36,738 (34.9%) had COPD

Table 2. Management and outcomes of stage I/II patients.

Characteristic		No COPD on Day Lung CA diagnosed (N = 6990)	COPD on Day Lung CA diagnosed (N = 5071)	P value
Overall Survival	N (%) Deaths	2629 (37.6)	2405 (47.4)	<0.001
	Median (95% CI) Mont			
	1-year (95% CI) OS			

Overall survival was worse among those with COPD
: HR 1.20, 95% CI 1.19-1.22

Table 3. Management and outcomes of stage III/IV patie

Characteristic		No COPD on Day Lung CA diagnosed (N = 19392)	COPD on Day Lung CA diagnosed (N = 11922)	P value
Overall Survival	N (%) Deaths	17222 (88.8)	10779 (90.4)	<0.001
	Median (95% CI) Months	5.3 (5.2, 5.5)	4.3 (4.1, 4.5)	
	1-year (95% CI) OS	29.8% (29.1, 30.4)	26.3% (25.5, 27.1)	

- **In Stage I/II Lung cancer**

✓ Less surgery : 56.8 vs 65.9%

✓ Less adj CTx : 15.4 vs 17.1%

✓ More Radiation : 26.0 vs 21.8%

- **In stage III/IV Lung cancer**

✓ less CTx : 55.9 vs 64.4%

✓ Less Radiation : 42.5 vs 47.5%

p for all <0.001

Goffin JR et al. PLoS One. 2021;16(5):e0251886.

Impact of emphysema on lung cancer survival

Table 3—*Adjusted Hazard for Lung Cancer Deaths and Lung Cancer Deaths According to the Extent of Emphysema*

Variables in the Model	HR	95% CI
Emphysema alone	2.3	1.6-3.4
Adjusted for:		
Age	2.1	1.5-3.2
Age and pack-y	1.8	1.2-2.7
Age, pack-y, and smoking status	1.7	1.1-2.5
According to extent of emphysema		
Mild	1.4	0.9-2.3
Moderate	1.8	0.9-3.4
Marked	3.2	1.5-6.7
Age	1.1	1.0-1.1
Pack-y	1.0	1.0-1.0
Current smoker or quit within 4 y	2.4	1.5-4.0
Former smokers who quit 5-10 y prior to study	1.3	0.6-2.7

See Table 2 for expansion of abbreviation.

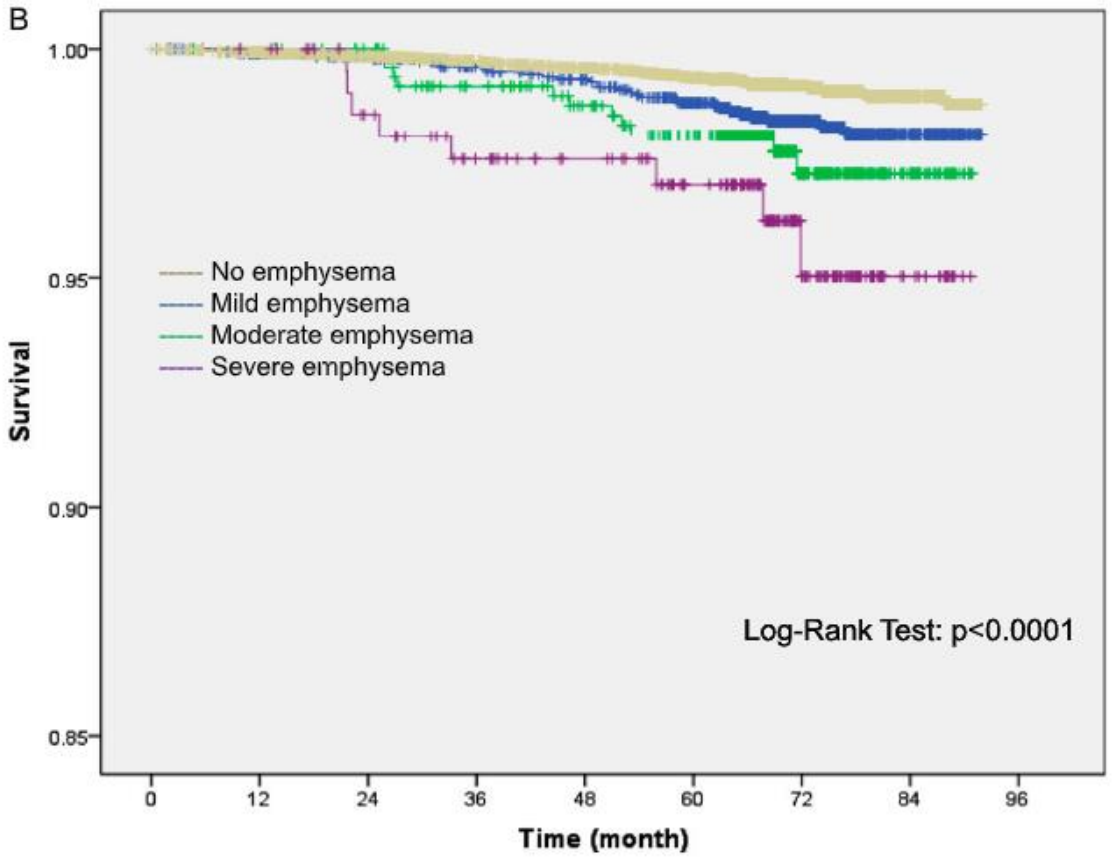


FIGURE 2. Kaplan-Meier curves showing an increase in lung cancer-specific mortality for subjects with emphysema on CT scans. A, Compared with those without emphysema. B, As the extent of emphysema increases.

- **Visual assessment of emphysema** on CT scan is a significant predictor of death from lung cancer

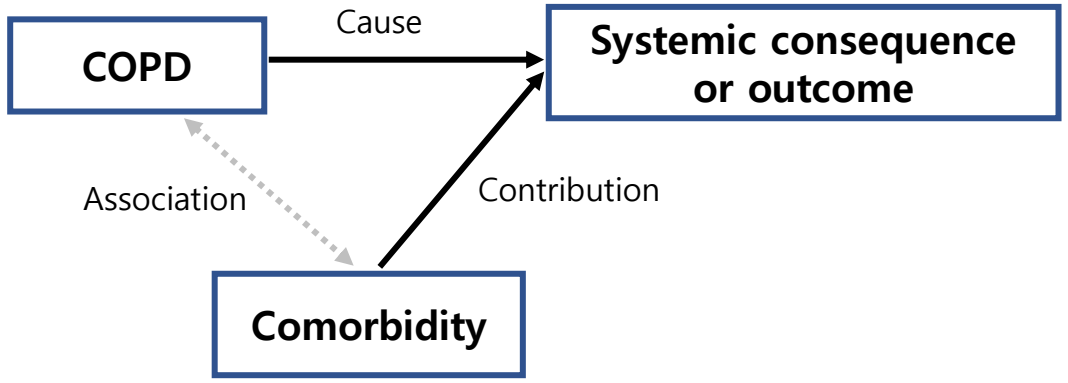
Zulueta JJ et al. CHEST 2012; 141(5):1216–1223

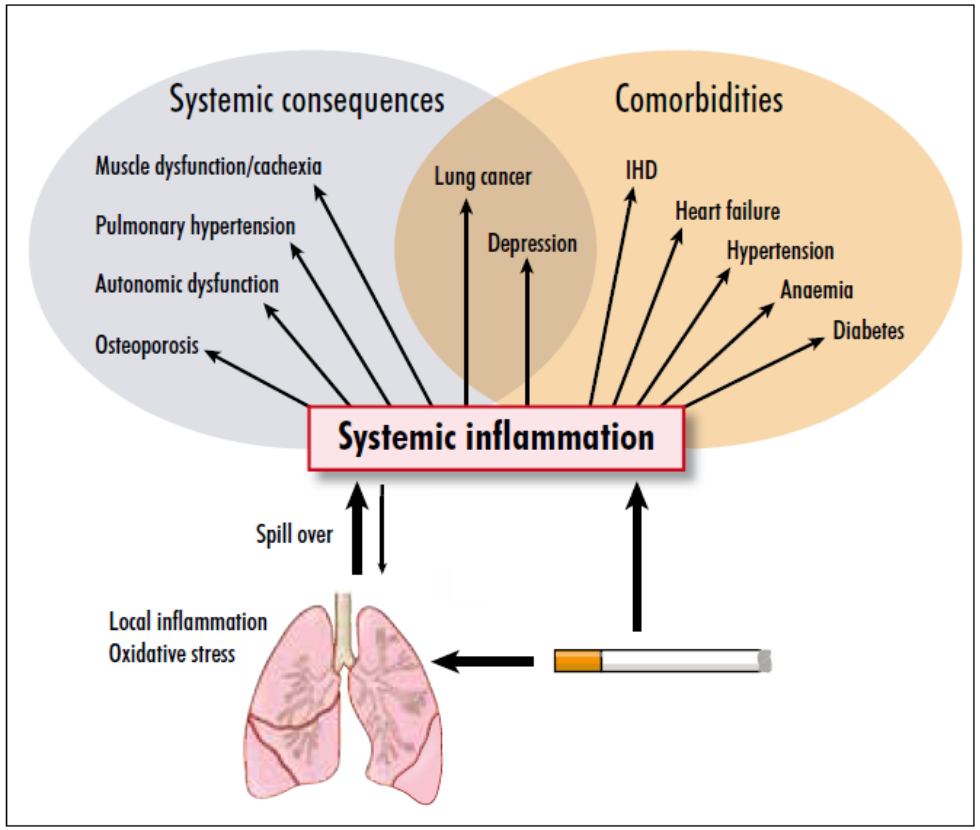
Content

- Introduction
- Pulmonary outcomes
- **Extrapulmonary outcomes**
  - ✓ **Clinical significance**
  - ✓ Cardiovascular disease
  - ✓ Pulmonary hypertension
  - ✓ Sarcopenia
  - ✓ Depression & anxiety
- Mortality : COPD related, all cause
- Prediction of prognosis

Interrelationships between COPD, comorbidities, and systemic outcome

- Comorbidities
- Extra-pulmonary or non-pulmonary manifestations
- Extra-pulmonary complications
- Systemic consequences of COPD





- **Complicates the management of COPD**
- **Increases morbidity and mortality of COPD**

DD Sin et al. Eur Respir J 2006; 28: 1245–1257
Rabinovich RA. Br J Hosp Med. 2011 Mar;72(3):137-45.

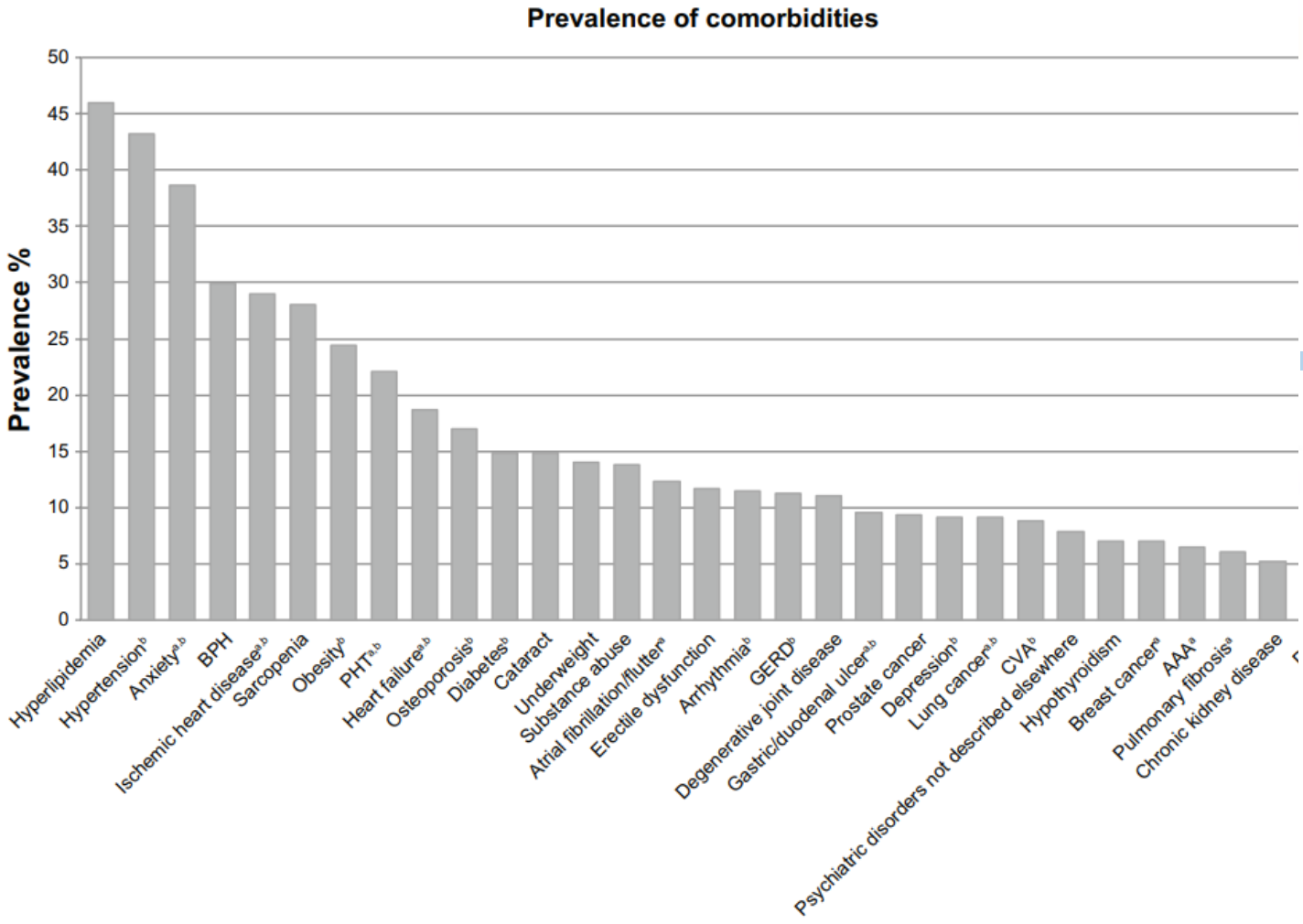
Link between COPD and systemic manifestations

- Nor clearly understood, multifactorial

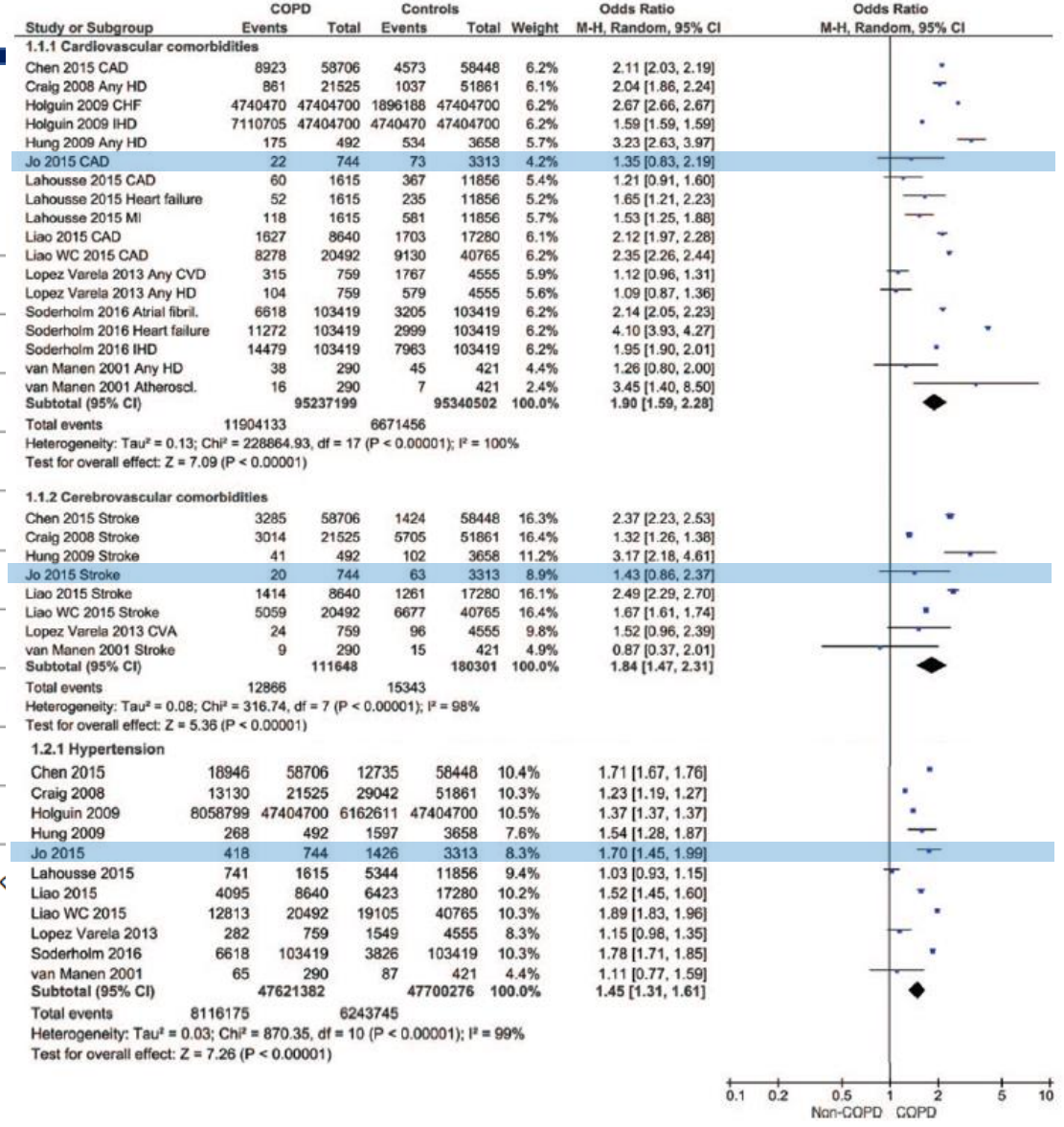
- **Systemic inflammation**
- **Inactivity / deconditioning**
- Hypoxemia, hypercapnia
- Malnutrition, electrolyte/fluid imbalance
- Endocrine disturbances: low testosterone, low IGF-1, GH resistance
- Suppression of erythropoiesis
- Risk factors for COPD : smoking, genetic pre-disposition
- Side-effects of treatments for COPD : steroids either inhaled or systemic, bronchodilators

Decramer M, et al. COPD. 2008;5(4):235-56.

Prevalence



Meta-analysis of 11 studies
(47,695,183 COPD vs 47,924,876 non-COPD control)

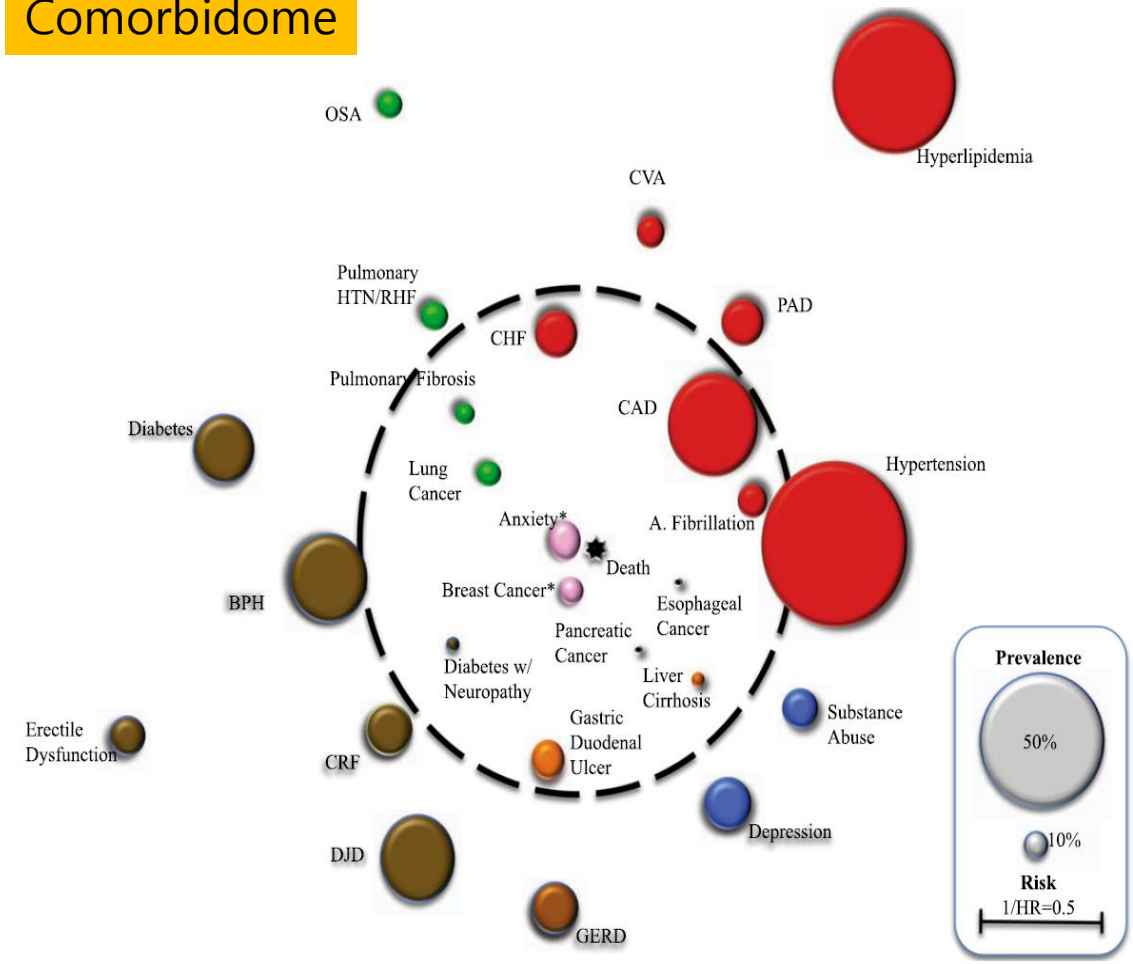


Smith MC, Wrobel JP. International Journal of COPD 2014:9 871–888
Yin HL et al. Medicine. 2017;95(19):e6836.

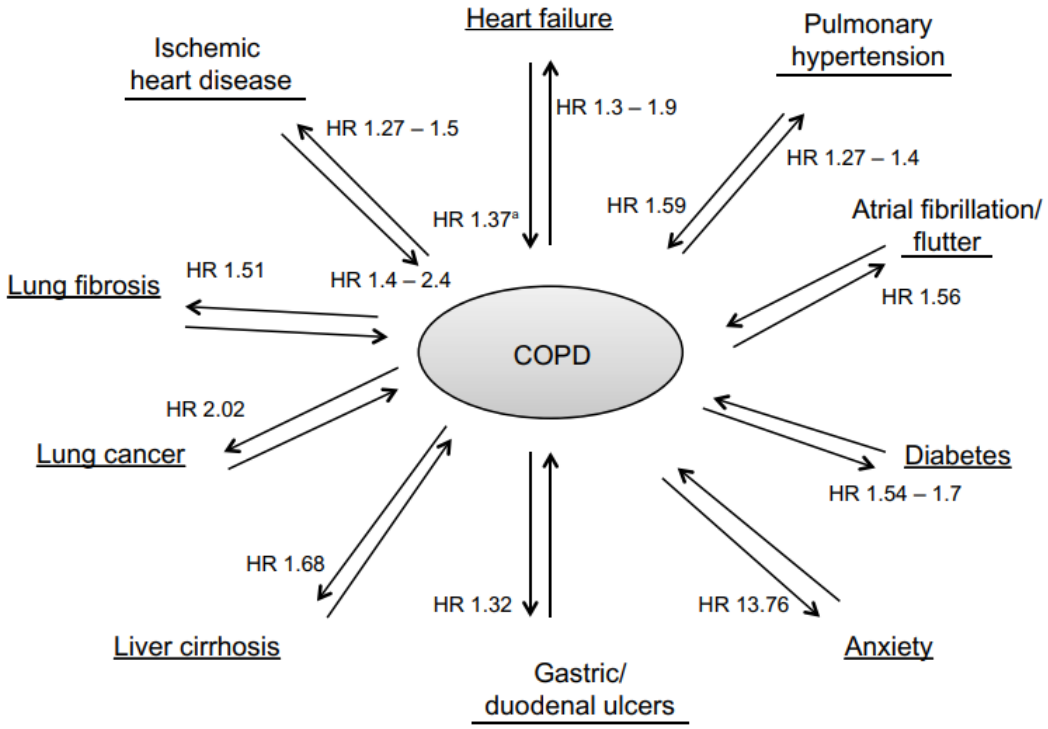
Impact of comorbidities on mortality

- 1,664 COPD patients, mean 6 comorbidities

Comorbidome



Impact on the mortality risk



Divo M et al. Am J Respir Crit Care Med. 2012;186(2):155-61.
Smith MC, Wrobel JP. International Journal of COPD 2014:9 871–888

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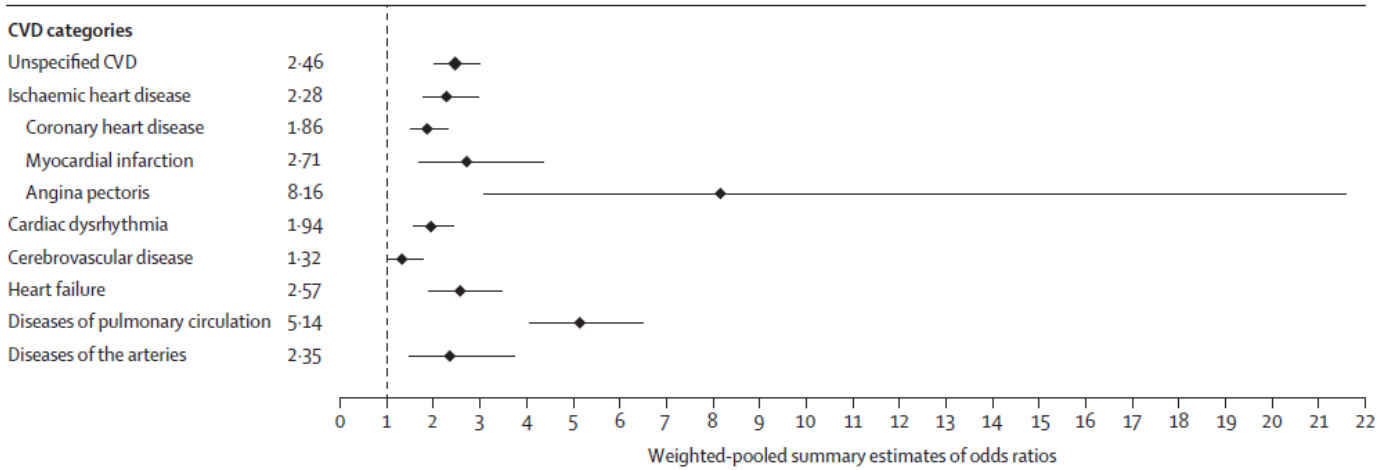
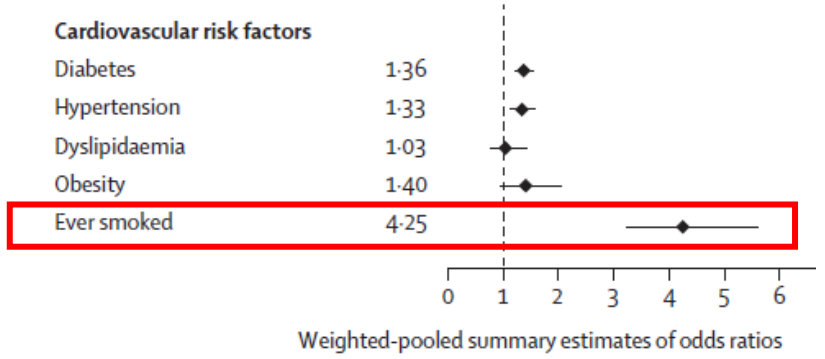
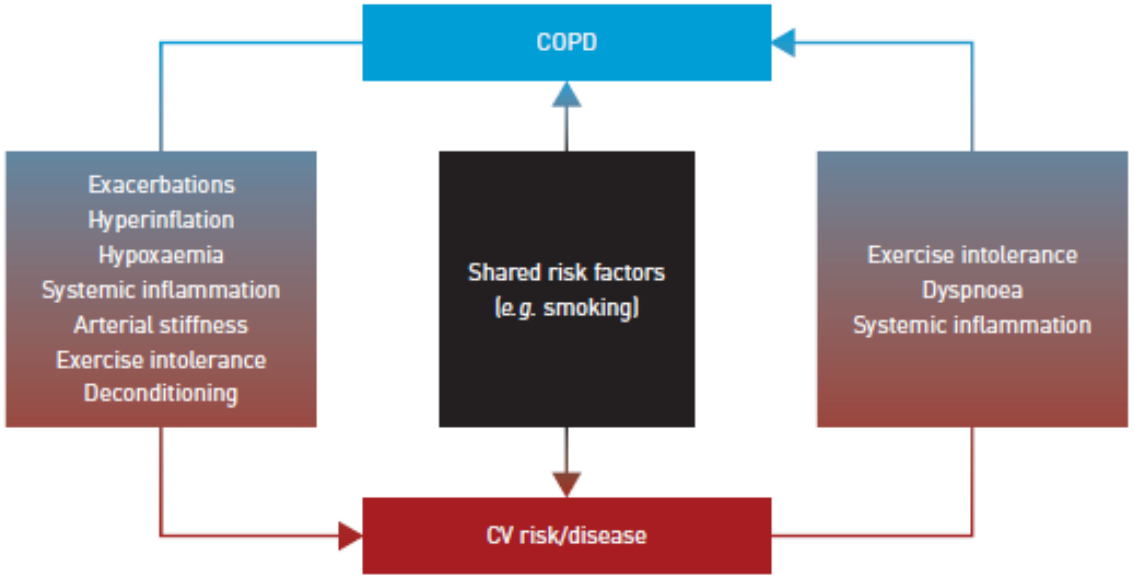
Cardiovascular disease and COPD



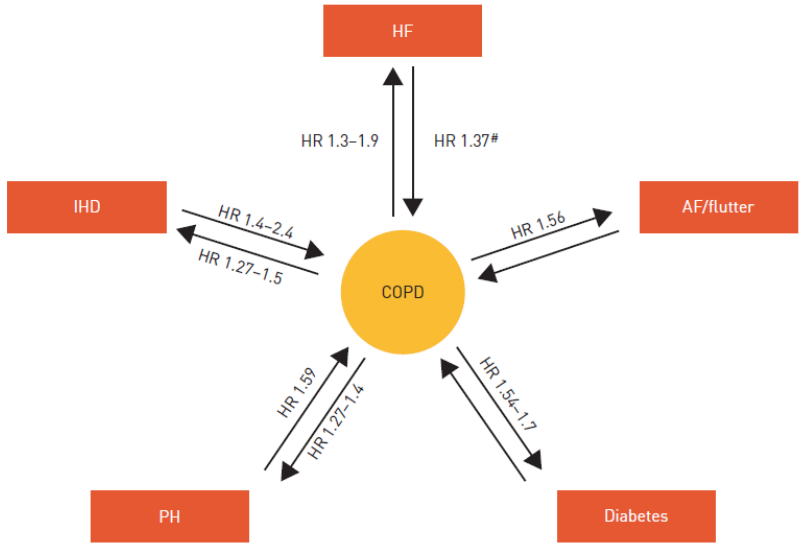
Meta-analysis of 27 studies



Potential interactions



Risk of mortality : inter-relation



Chen W et al. Lancet Respir Med 2015; 3: 631–39
Fabe KF et al. Eur Respir Rev 2018; 27: 180057

β-receptor on cardiovascular and respiratory system

β1

Heart

β2

Lungs

Leg blood vessels

Effect of β-agonists	✓ Increased inotropy and chronotropy	✓ Bronchodilation ✓ Vasodilation
Effect of β-blockers	✓ Reduction in HR, contractility and Cardiac output ✓ Beneficial in heart disease (heart failure, ischemic heart disease)	✓ Risk of bronchoconstriction ✓ Risk of vasoconstriction or worsening of ischemia

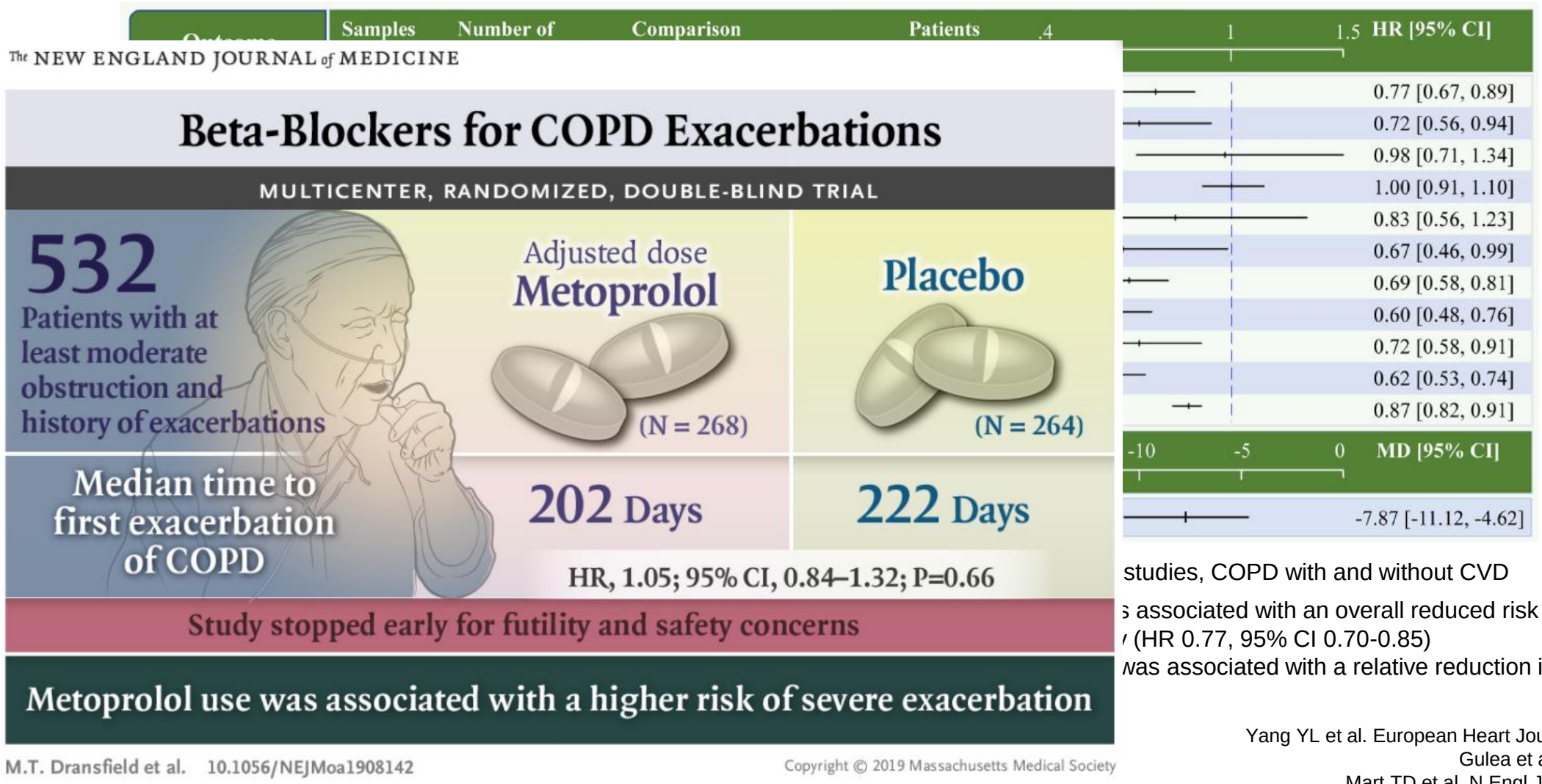
Concerns about β-blocker use in COPD

Selective β-blockers	Non-selective β-blockers
✓ Atenolol	✓ Propranolol
✓ Metoprolol	✓ Nadolol
✓ Carvedilol	✓ Sotalol
✓ Nebivolol	

Baker JG, Wilcox RG. Thorax 2017;72:271–276.

β-blocker in patients with COPD and CVD

Meta-analysis of 49 studies
Effect of BB on outcomes in patietns with COPD with CVD



studies, COPD with and without CVD

s associated with an overall reduced risk of AECOPD
/ (HR 0.77, 95% CI 0.70-0.85)
was associated with a relative reduction in FEV1 versus

Yang YL et al. European Heart Journal (2020) 41, 4415–4422
Gulea et al. Respir Res (2021) 22:64
Mart TD et al. N Engl J Med 2019; 381:2304-2314

Impact of COPD treatment on CVD

LABA

- Stimulation of sympathetic drive
- Increase heart rate
- Reduce K concentration

➔ risk of CVD and arrhythmias

➢ **SUMMIT study (n=23,835)**

✓ Cardiac event 17% in placebo, 18% in FF/vilanterol, 17% in FF, 17% in Vilanterol group

❖ Decrease IC & hyperinflation

❖ Improve dyspnea and oxygen delivery

❖ RV compliance

Lancet 2016;387:1817-26.
Int J Chron Obstruct Pulmon Dis 2015;10:1917-23.
Thorax 2010;65:588-93.

✓ Caution for arrhythmias is needed for high dose **theophylline** (serum concentration >30mg/L) , However, daily dose of 400mg reached serum concentration around <15 μg/ml and didn't related to cardiac adverse events

CHEST 1990;98(3):672-8.
Resp Med 2004;98(10):1016-24.

LAMA

- Inhibition of parasympathetic drive

➔ Arrhythmogenic

➢ **UPLIFT study (n=5993)**

✓ Cardiac mortality, HR = 0.86 (95% CI, 0.75-0.99)

❖ Improve hyperinflation

❖ Improve vascular stiffness

Am J Respir Crit Care Med 2009;180:948-55.
Respir Med 2007;101:2017-24.
Chest 2014;146:1521-30.

ICS

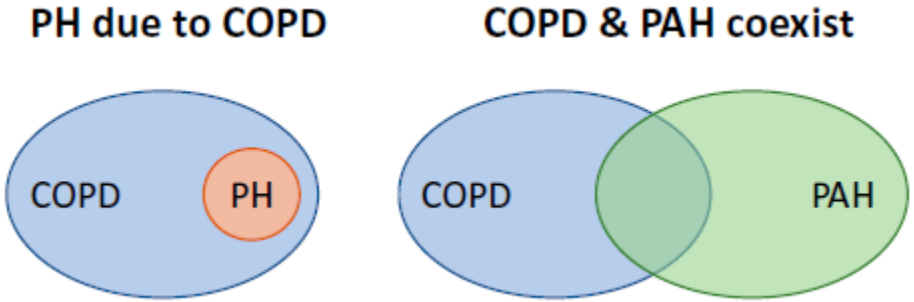
- Precipitating atherogenesis vs recovery of vascular endothelium and occlusion

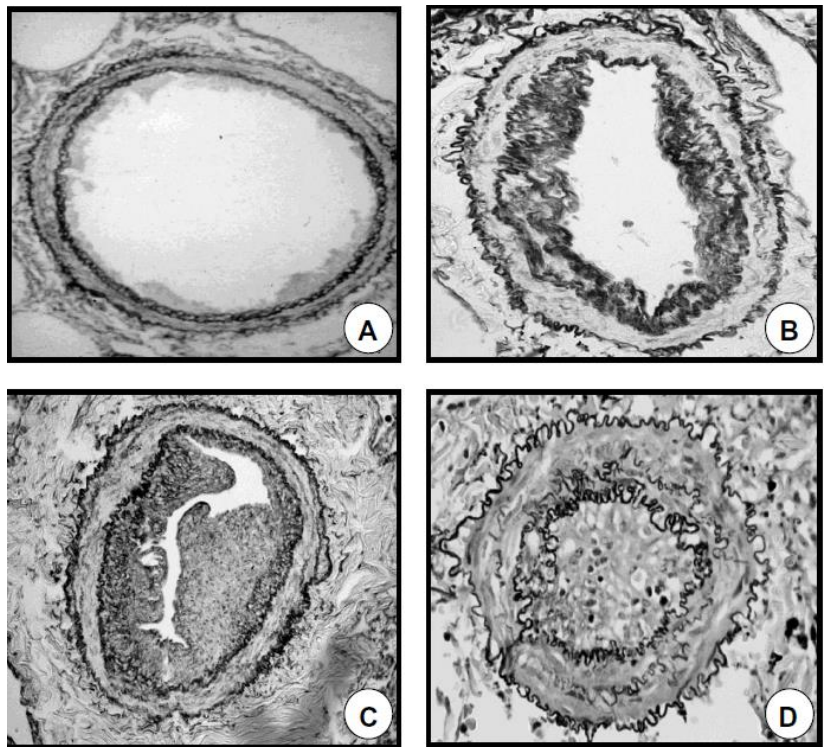
➢ **TORCH study (n=6184)**

✓ Cardiovascular event 24.2% in placebo, 22.7% in salmeterol, 24.3% in FP, 20.8% in FP/Salmeterol group

Thorax 2010;65:719-25

Pulmonary hypertension (PH) in COPD





- **Prevalence of COPD-PH**
  - ✓ Severity of the disease
  - ✓ Definition of PH
  - ✓ Method of diagnostic assessment.

- ➢ GOLD stage IV : 90% have mPAP >20 mmHg
- ➢ 1-5% of COPD have mPAP >35-40mmHg at rest

Chaouat A et al. Am J Respir Crit Care Med 2005; 172: 189–194.
Blanco I et al. Int J Chron Obstruct Pulmon Dis. 2020;15:1315-1324.

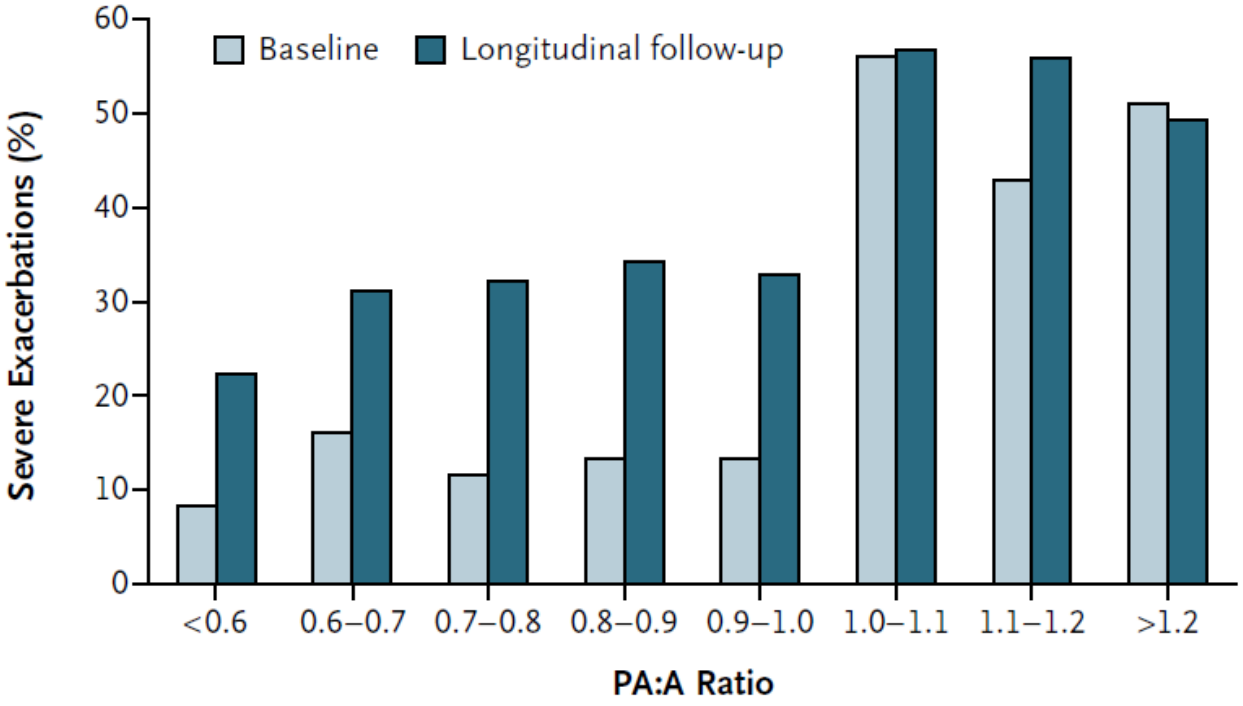
Impact of COPD-PH on exacerbation

COPDGene study

PA:A > 1 (n=819) vs PA:A ≤ 1 (n=2,645)

Table 2. Factors Independently Associated with Exacerbations at Enrollment and Follow-up.*

Time Period and Factor	Odds Ratio (95% CI)	P Value
History of severe exacerbations at enrollment		
PA:A ratio >1	4.78 (3.43–6.65)	<0.001
Severe exacerbations during longitudinal follow-up		
PA:A ratio >1	3.44 (2.78–4.25)	<0.001
All exacerbations during longitudinal follow-up		
PA:A ratio >1	1.86 (1.54–2.24)	<0.001

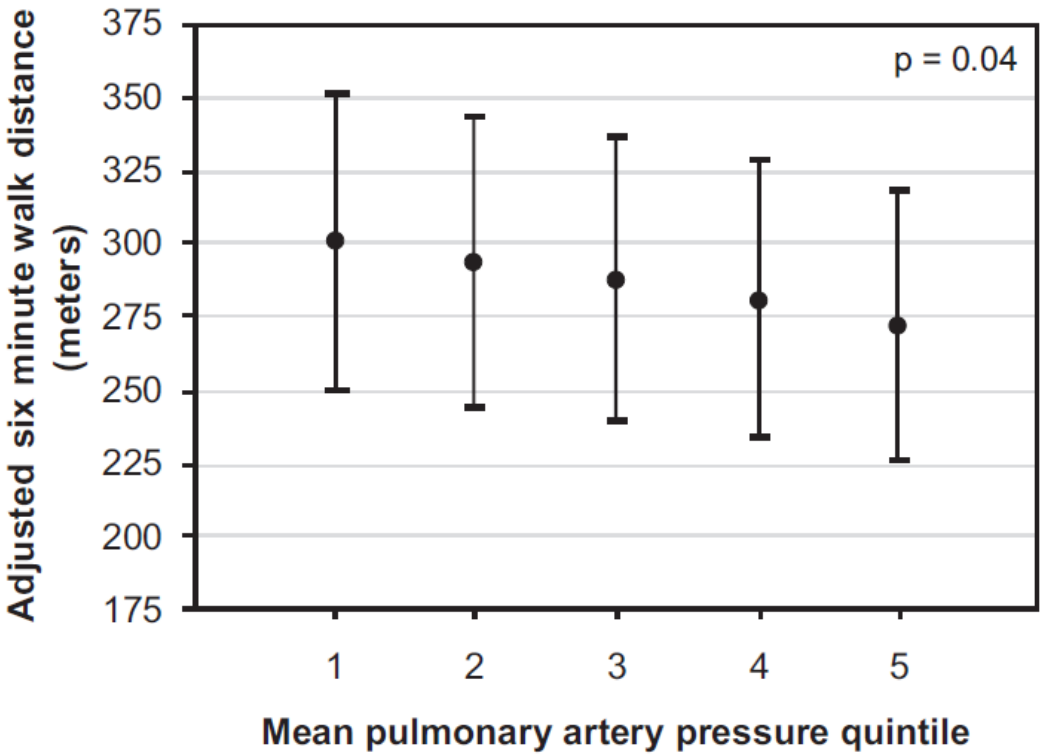


- Pulmonary artery enlargement (PA:A ratio of >1) was associated with severe exacerbation of COPD

Wells JM et al. N Engl J Med. 2012;367(10):913-21.

Impact of COPD-PH on exercise function

- 362 COPD patients referred for lung transplantation
- Definition of PH by cardiac catheterization : mPAP >25 mmHg & PAOP <16mmHg
- Prevalence of PH : 23%



Higher mPAP was associated with

✓ Lower FVC & FEV1

✓ Higher Pco2, lower Po2

✓ More Rt heart dysfunction

Higher mPAP was associated with **shorter 6MWD**

: -11 m for every 5 mmHg rise in mPAP

(95% CI, -21 to -0.7; p=0.04)

Sims MW et al. CHEST 2009; 136:412–419

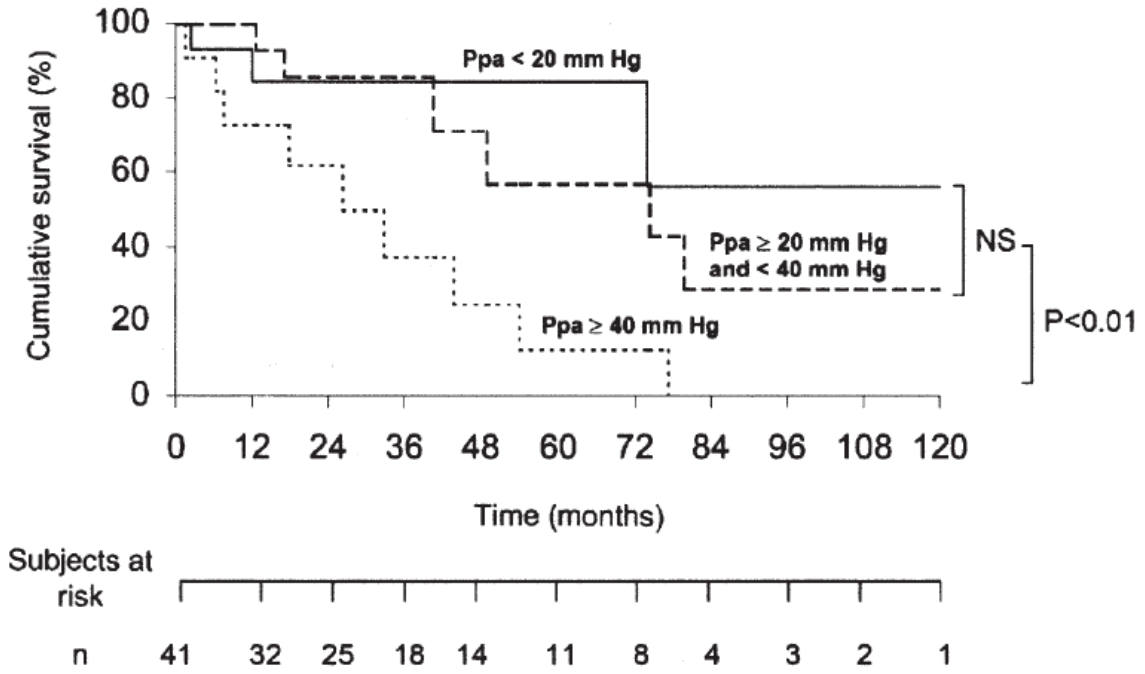
Impact of COPD-PH on mortality

998 COPD patients with chronic respiratory failure underwent Rt heart catheterization

27 had Ppa ≥ 40 mmHg : 11 attributed to COPD after exclusion of other cause of PH

Dependent Variable	Independent Variable	n	Coefficient	p
Ppa	VC	30	−0.344	= 0.063
	FEV_1	30	−0.469	= 0.009
	FEV_1/VC	30	−0.236	= 0.210
	DL_{CO}	22	−0.228	= 0.306
	ES	29	0.175	= 0.365
	Pa_{O_2}	30	−0.655	< 0.001
	Pa_{CO_2}	30	0.487	= 0.006
ES	DL_{CO}	22	−0.727	< 0.001
	TLC	24	0.336	= 0.108

Definition of abbreviations: DL_{CO} = diffusing capacity for carbon monoxide; ES = emphysema score; Ppa = pulmonary artery mean pressure; $Q_{S/T}$ = right-to-left shunt; TLC = total lung capacity.



Chaouat A et al. Am J Respir Crit Care Med 2005; 172: 189–194.

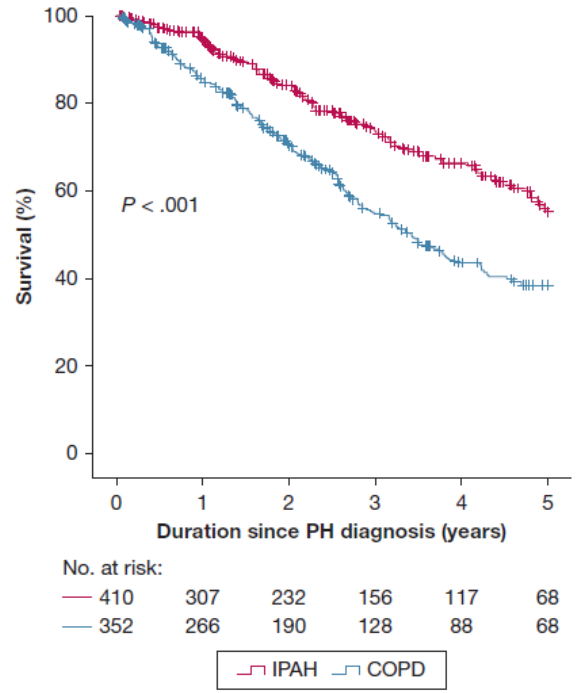
PAH targeted therapy in COPD-PH

Are medications designed to treat iPAH capable of improving hemodynamics in PH-COPD ?

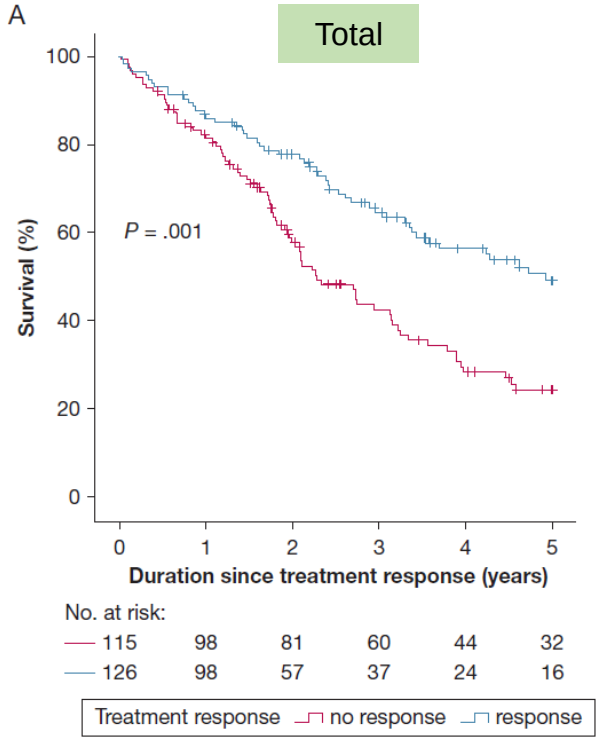
Worsen VQ matching by pulmonary vasodilation ?

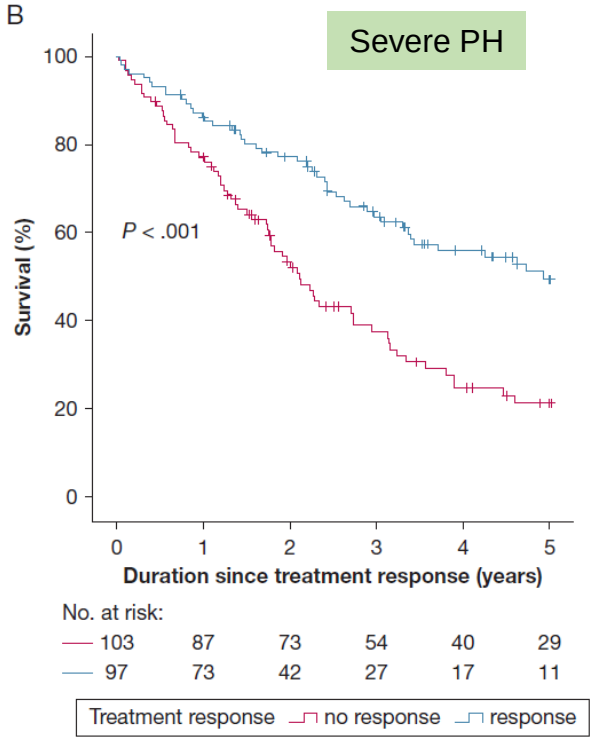
Effect of PAH-targeted therapy on COPD-PH

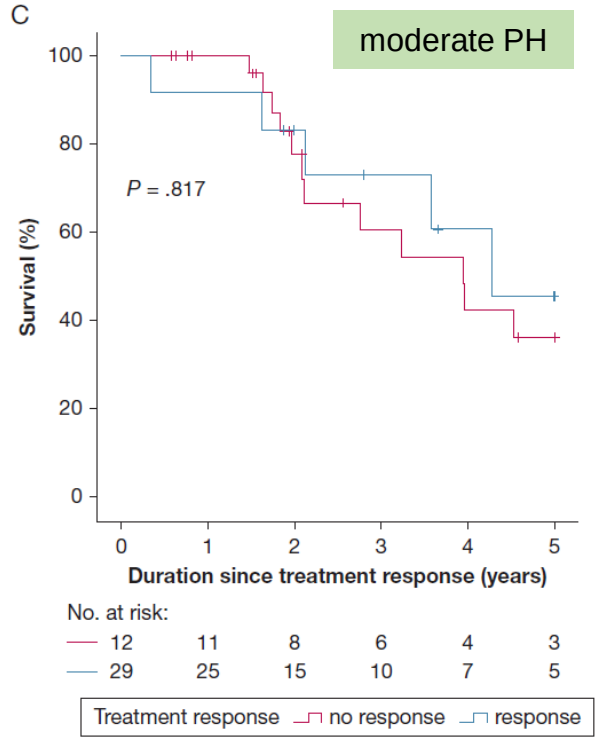
5-yr survival of IPAH and PH-COPD



5-yr survival of PH-COPD with and without treatment response







- Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension **(COMPERA)**

✓ PH-COPD group was functionally more impaired and had a poorer outcome than IPAH group

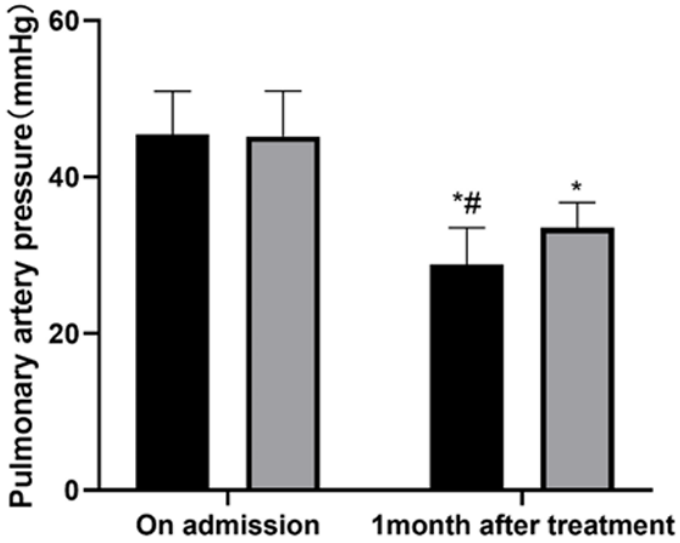
✓ Risk factors for poor outcome in PH-COPD

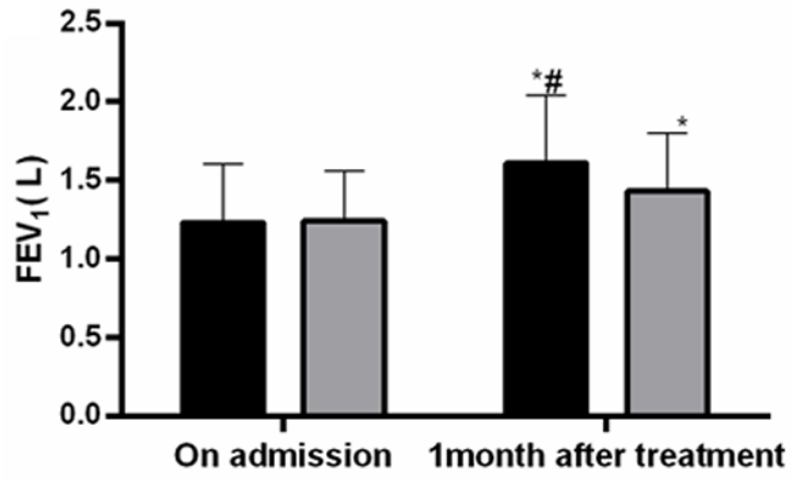
: male sex (RR 1.54), low 6MWD (per 10m, RR 0.97), and high PVR (per 1 Wood unit, RR 1.06)

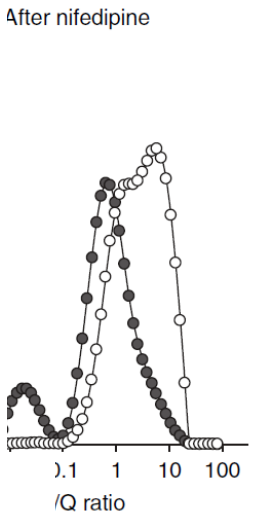
✓ Responder (improvement in 6MWD by ≥ 30m or WHO FC) → better outcomes

Vizza CD et al. Chest. 2021;160(2):678-689.

Safety of PAH-targeted therapy on COPD-PH



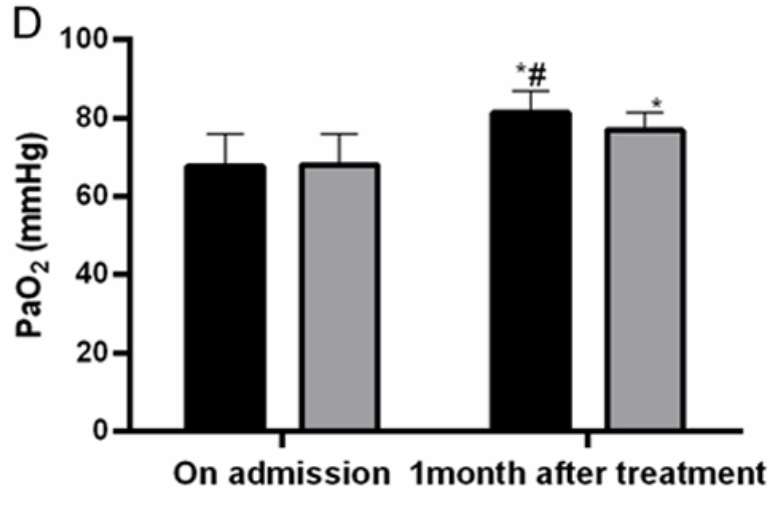


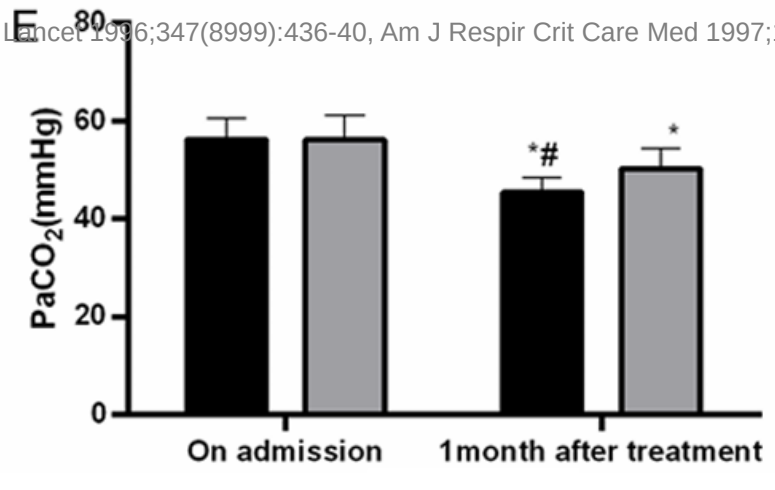


Group A Bosentan + sildenafil (n=50)

Group B Bosentan + iloprost (n=40)

Barberà JA, Blanco I. Drugs. 2009;69(9):1153-71.





Lancet 1996;347(8999):436-40, Am J Respir Crit Care Med 1997;156:800-6, Thorax 1997;52(2):120-4.

–628

75.

)-5.

on Dis. 2017;12:3353-3360.

Li Y et al. Am J Transl Res 2021;13(10):11522-11530.

Recommendation for PH-COPD for better outcome

- **Long-term oxygen therapy**

✓ Indication : PaO_2 55-60 mmHg, or SaO_2 of 88%, evidence of PH, CHF, polycythemia

➢ In stabilized hypoxemic COPD patients, LTOT for
  - 15 h/day: prevents the progressive increase of PAP
  - >18 h/day: slight decrease of PAP

- LTOT is the most appropriate treatment for PH-COPD associated with respiratory failure, although it has little impact on pulmonary hemodynamics and does not reverse the pathological lesions of the pulmonary circulation.

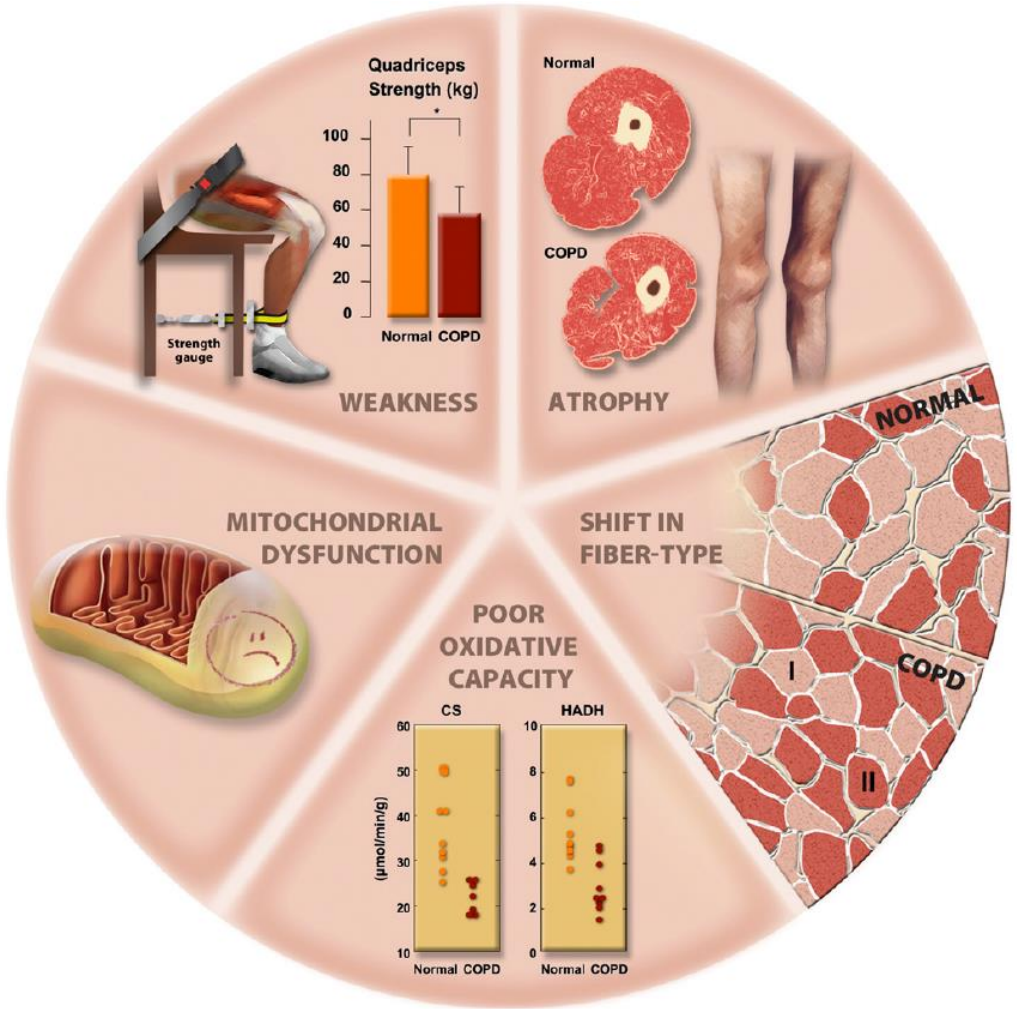
- **Exercise rehabilitation**

- Improve exercise capacity, irrespective if patients received sildenafil or placebo

- **Transplantation**

GOLD 2021
Long-term Oxygen Treatment Trial Research Group. N Engl J med. 2016;375(17):1617-1627.
Grunig E et al. Eur Respir J. 2019;53(2):1800332.

Morphological and structural alteration in limb muscle of COPD



- **Prevalence** : higher than general population, 15% to 55%

- **Suggested mechanism of sarcopenia in COPD**
  - ✓ Effect of tobacco
  - ✓ Disuse, inactivity
  - ✓ Poor peripheral oxygenation
  - ✓ Inflammation triggering of the muscle proteolysis
  - ✓ Oxidative stress
  - ✓ Hypercapnia
  - ✓ Diminished effect of anabolic hormones (GH, T)
  - ✓ Corticosteroids
  - ✓ Malnutrition
  - ✓ Vit D deficiency

Maltais F et al. Am J Respir Crit Care Med. 2014;189(9):e15-62.
Jones SE et al. Thorax. 2015;70(3):213-8.
Clin Pulm Med 2007;14(3):117–26
Am J Respir Crit Care Med 2010;182(4):477–88
Am J Respir Crit Care Med 2015;191(6):620-625
Thorax 2011; 66(11): 961–969

Impact of sarcopenia in COPD

	Any Event at Baseline (Rate Ratio)	Any Event during Follow-Up (Rate Ratio)	Any Severe Event during Follow-Up (Rate Ratio)
Handgrip strength (per 1 kg decrement)	1.05 (1.01–1.08)	1.04 (1.01–1.07)	1.06 (1.01–1.12)
Lung function			
FEV_1% predicted	0.99 (0.98–1.00)	0.99 (0.98–1.01)	0.99 (0.98–1.01)
Chronic bronchitis	1.33 (0.80–2.20)	0.82 (0.48–1.40)	0.58 (0.22–1.50)
Exacerbations at baseline	N/A	1.18 (1.00–1.38)	1.29 (1.01–1.65)

COPDGene cohort with handgrip strength (n=272)
- HGS showed correlation with body composition markers on chest CT
- Lower the HGS, higher the exacerbation risk

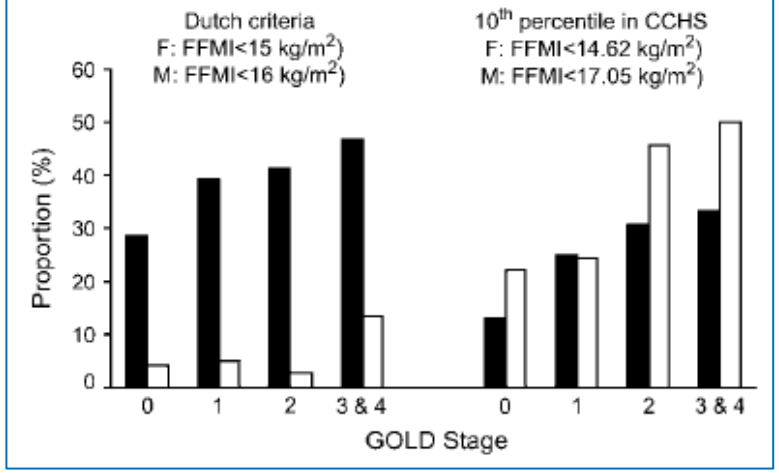


TABLE 2. MORTALITY RISK ASSOCIATED WITH LOW FAT-FREE MASS INDEX AND LOW BODY MASS INDEX

	Low FFMI†	Low BMI‡
All subjects with COPD		
Overall mortality	1.5 (1.2–1.8)	1.8 (1.3–2.7)
COPD mortality	2.4 (1.4–4.1)	3.2 (1.5–7.0)
Subjects with normal BMI*		
Overall mortality	1.3 (1.1–1.7)	—
COPD mortality	2.0 (0.9–4.5)	—

COPD in Copenhagen general population cohort (m=1899)
- Low FFMI in more severe COPD
- Increased risk of mortality in low FFMI group

Martinez CH et al. A*nn Am Thorac Soc*. 2017;14(11):1638-1645.
Vestbo J et al. Am J Respir Crit Care Med 2006;173(1):79–83

Impact of sarcopenia therapy on COPD

Treatment	Mass	Strength	Exercise tolerance	QoL	Dyspnea	Survival	Background
Exercise	Favorable	Favorable	Favorable	Favorable	Favorable		Eur Respir J 2012; 40(2):338-44 123-125, 121, 126
Supplemental oxygen			Favorable			Favorable	Emtner M et al. Am J Respir Crit Care Med. 2003;168(9):1034-42. Maltais F et al. Am J Respir Crit Care Med 2014;189(9):e15-62
Nutrition + exercise	Favorable	Favorable	Favorable				Creutzberg EC et al. Nutrition 2003;19:120–127 Van Wetering CR et al. J Am Med Dir Assoc 2010;11: 179–187.
Nutrition + exercise + anabolic hormone supplementation	Favorable	Favorable	Favorable	Favorable		Favorable	Pison CM et al. Thorax 2011;66:953-960 Rondanelli M et al. Am J Clin Nutr. 2016;103(3):830-40
Anabolic steroids	Favorable	Favorable	Favorable	Favorable			Pan L et al. PLoS One. 2014 Jan 10;9(1):e84855. Creutzberg EC et al. Chest. 2003;124(5):1733-42
Growth hormones	Favorable						Pape GS et al. Chest. 1991 99(6):1495-500. Maltais F et al. Am J Respir Crit Care Med. 2014 May 1;189(9):e15-62.
Ghrelin	Favorable	Favaroble	Favorable				Passey SL et al. 2016 Oct;166:56-70. White HK et al. J Clin Endocrinol Metab 2009;94:1198–1206
Myostatin inhibition	Favorable						Rolkey MI et al. Am J Respir Crit Care Med. 2019;199(3):313–320.
Vitamine D	Favorable						Bauer JM et al. J Am Med Dir Assoc 2015;16(9):740-7

Neuromuscular electrical stimulation (NMES)

- Electrical stimulation of isolated muscle, evoking involuntary contraction
- Portable, non-invasive and Passive form of exercise training
- Add-on interventions during pulmonary rehabilitation

Table 3
Studies investigating the efficacy of neuromuscular electrical stimulation for treating muscle wasting in COPD.

Study population	Training protocol	Effects of NMES	Reference
After AECOPD (hospitalized)	35 Hz, 1 h per day, 5 days/week for 6 weeks. Both legs, hamstrings and quads.	Increased MVC and 6MWD, reduced muscle protein carbonylation (and reduced myosin heavy chain carbonylation); fiber type shift (increased Type I, decreased Type IIx).	Abdellaoui et al., 2011
During AECOPD	50 Hz, 30 min, 1× per day for 14 days. One leg only, quads and vastus medialis.	Increased quadriceps MVC in NMES treated leg (untreated leg decreased MVC)	Giavedoni et al., 2012
COPD	50 Hz, 30 min daily for 6 weeks. Both legs, quads only.	Increased 6MWD and MVC in NMES group vs placebo. Increased quad CSA.	Maddocks et al., 2016
COPD (moderate to severe, FEV_1 < 50% predicted)	50 Hz, 30 min per day, 5 days per week for 6 weeks. Both legs.	Increased quad strength (peak torque)and endurance (decreased fatigue). Reduced dyspnea.	Neder et al., 2002
COPD (severe to very severe, FEV_1 < 35% predicted)	HF-NMES (75 Hz) or LF-NMES (15 Hz), 18 min 2× per day, 5 days per week for 8 weeks.	Increased quad peak torque after HF-NMES but not LF-NMES. Increased endurance (total work) in HF-NMES and LF-NMES, but greater increase with HF-NMES. Reduced dyspnea.	Sillen et al., 2014
COPD (moderate to severe FEV_1 < 40% predicted)	50 Hz, 60 min, 2× per day, 5 days per week for 8 weeks. Both legs, quads.	Increased FEV_1 and exercise tolerance, reduced dyspnea. Increased 6 MWD. Increased fat-free mass, muscle mass and thigh CSA. Reduced TNFα and increase β-endorphin levels.	Vieira et al., 2014
COPD (severe)	50 Hz, 35 min quads, 25 min calves, 5× per week for 6 weeks. Both legs.	Increased mid-thigh and calf muscle CSA, improved strength and 6MWD (apart from 6 non-responder patients). Downregulation of catabolic protein atrogin-1, increase in anabolic pathway protein p70S6K.	Vivodtzev et al., 2012
COPD (moderate to severe, FEV_1 < 60% predicted, except 1 patient)	50 Hz, up to 1 h/eg, 5× per week for 6 weeks. Both legs, quads.	No significant effect of NMES on leg muscle mass, peak torque and 6MWD. Significant increase in Type II fiber CSA and a decrease in Type I fiber CSA—no changes in relative proportion of fiber types.	Dal Corso et al., 2007

Abbreviations: MVC, maximal voluntary contraction; 6MWD, 6 minute walk distance; CSA, cross-sectional area; HF-NMES, high-frequency NMES; LF-NMES, low-frequency NMES.

Vanfleteren LEGW, et al. Respirology. 2019;24(9):899-908
Passey SL et al. Pharmacol Ther. 2016 Oct;166:56-70

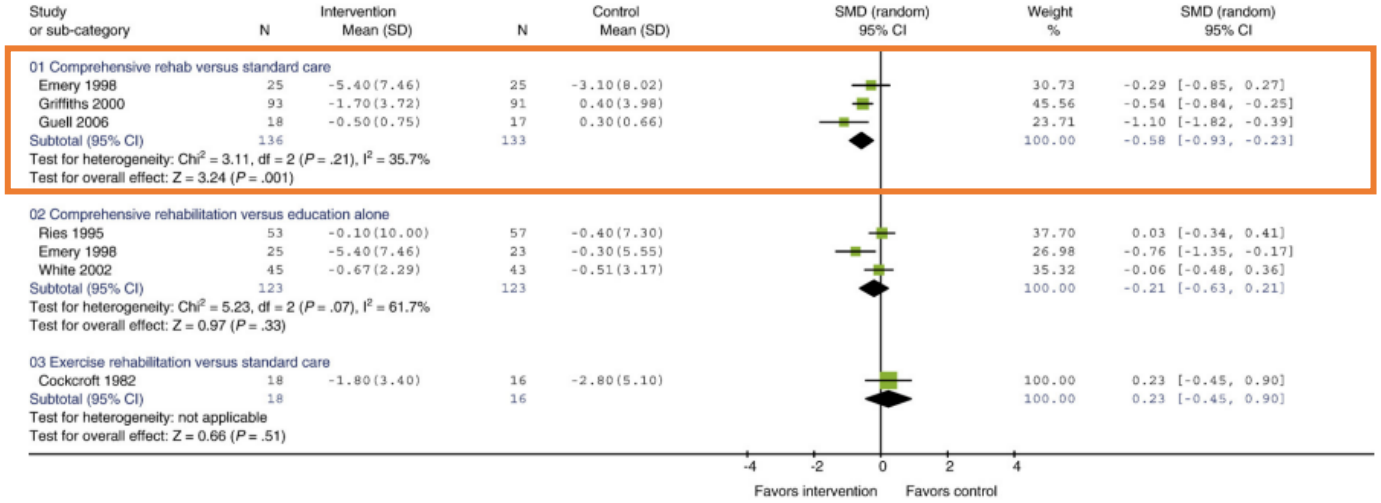
Depression, anxiety

- **Prevalence** : 19.6% in the mild to moderate group, 25% in the severe group, F > M

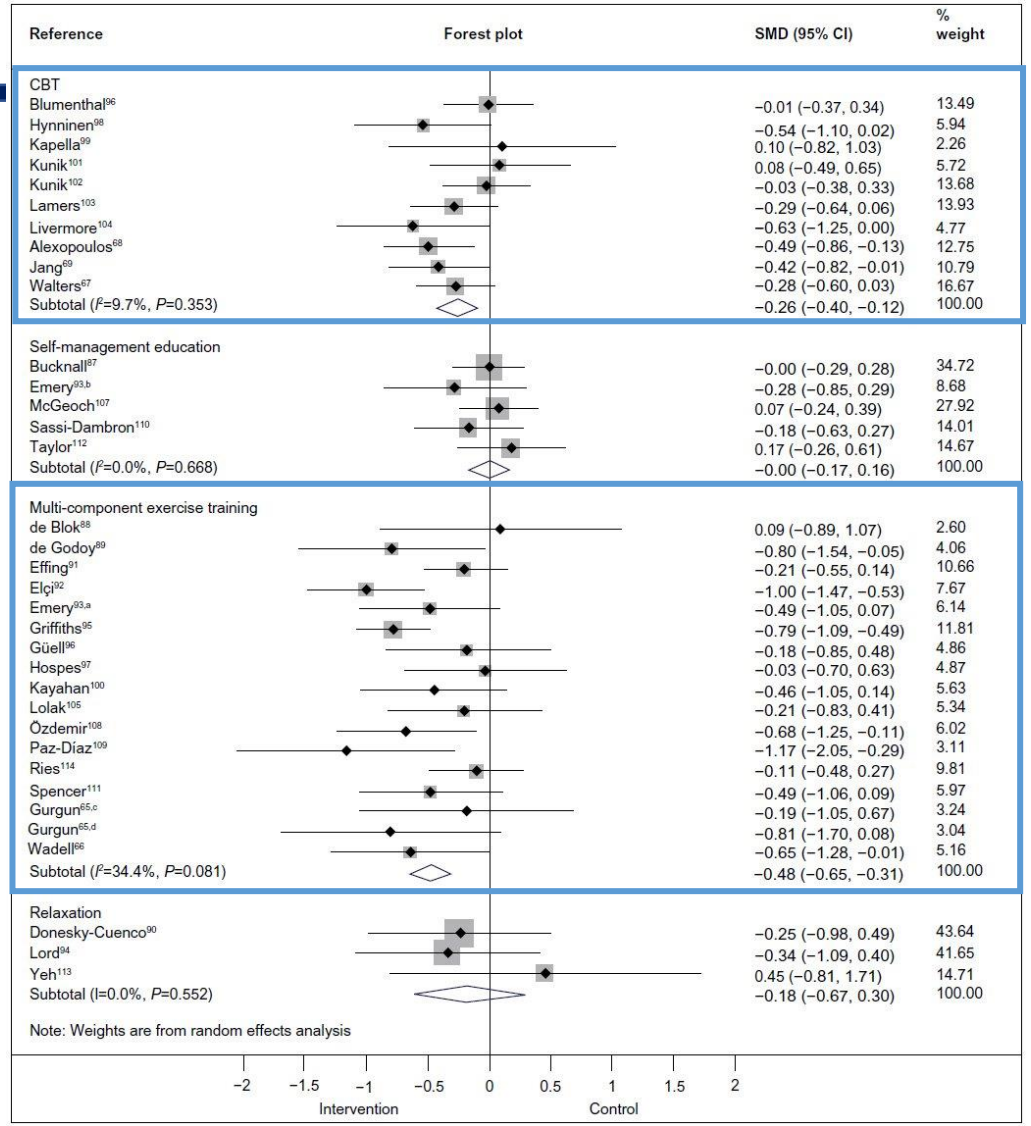
- **Clinical importance**
  - ✓Impaired QoL, reduced social interaction
  - ✓Impaired exercise capacity, increased physical disability
  - ✓Increased exacerbation risk
  - ✓Increase health care utilization rates and costs
  - ✓Increased mortality risk

Yohannes AM et al. Eur Respir Rev. 2014;23(133):345-9

Depression, anxiety



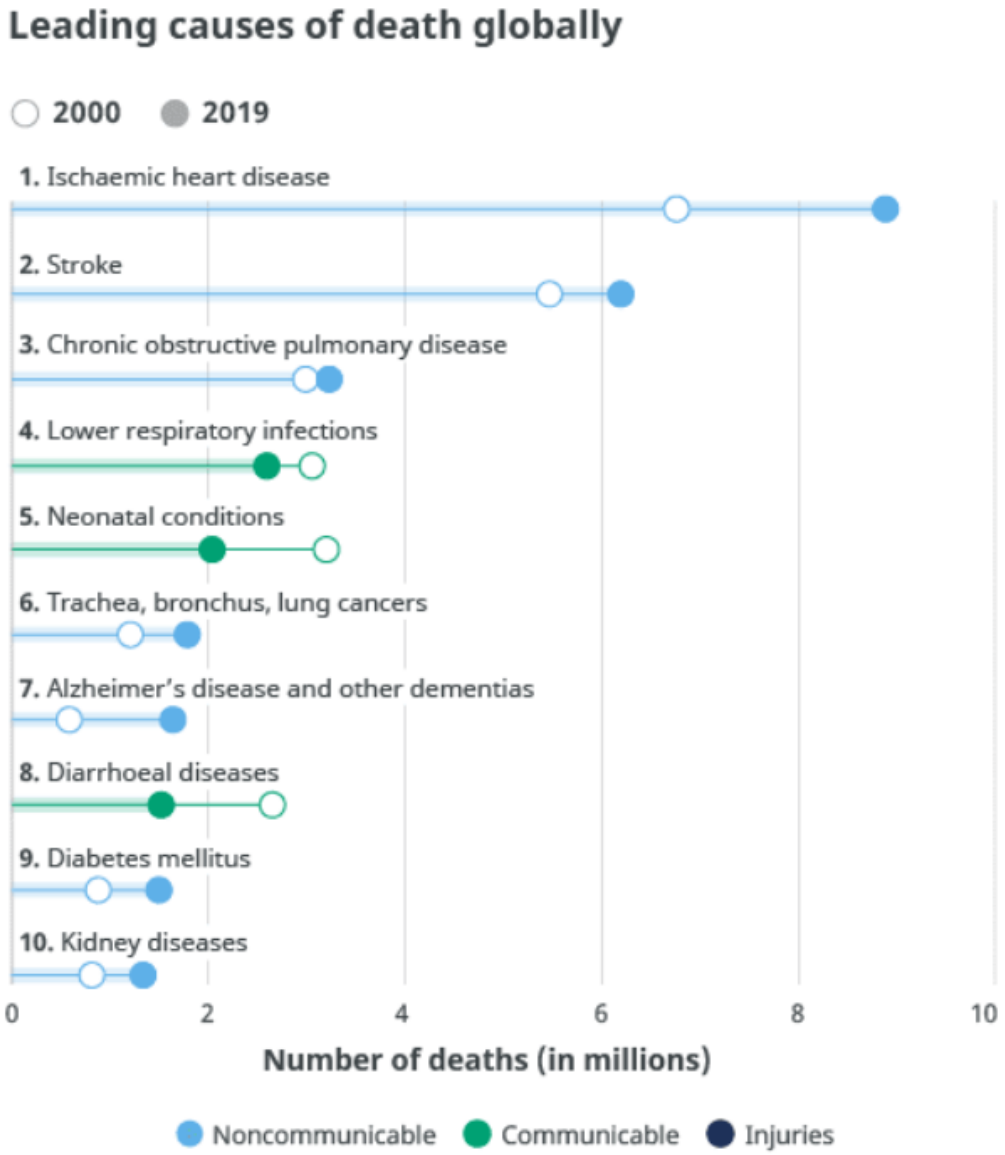
- Comprehensive pulmonary rehabilitation : effective
- Cognitive behavioral therapy : effective
- Multi-component exercise training : effective
- Anti-depressant drugs : inconclusive



Coventry PA et al. J Psychosom Res. 2007;63(5):551-65.
Vozoris NT et al. Eur Respir J. 2018 Jul 27;52(1):1800475.
Yohannes AM et al. Drugs Aging (2014) 31:483–492
Panagioti M et al. Int J Chron Obstruct Pulmon Dis. 2014;9:1289-306.

Trends of global mortality

The top 10 causes of death from WHO



Mortality risk of COPD and reduced lung function

Table 2
Associations between chronic obstructive pulmonary diseases and natural-cause mortality.

COPD	No. of deaths (Mortality rate[c])	Model 1[d] Hazard ratio (95%CI)	*P*	Model 2[d] Hazard ratio (95%CI)	*P*	Mode 3[d] Hazard ratio (95%CI)	*P*
COPD classifications [a]							
Normal	12,083 (3.0)	Reference	–	Reference	–	Reference	–
Restricted	12,944 (7.5)	1.63 (1.59, 1.68)	<0.001	1.32 (1.29, 1.36)	<0.001	1.31 (1.27, 1.35)	<0.001
GOLD I	180 (8.9)	1.53 (1.30, 1.80)	<0.001	1.18 (1.00, 1.39)	0.045	1.18 (1.00, 1.39)	0.045
GOLD II	1,534 (11.0)	2.09 (1.98, 2.22)	<0.001	1.44 (1.36, 1.53)	<0.001	1.43 (1.35, 1.51)	<0.001
GOLD III	1,082 (16.6)	2.68 (2.51, 2.86)	<0.001	1.81 (1.07, 1.94)	<0.001	1.78 (1.66, 1.90)	<0.001
GOLD IV	460 (25.0)	3.39 (3.08, 3.73)	<0.001	2.19 (2.00, 2.41)	<0.001	2.13 (1.94, 2.34)	<0.001
Trend test	–	1.28 (1.27, 1.30)	<0.001	1.15 (1.14, 1.17)	<0.001	1.15 (1.14, 1.16)	<0.001
Overall COPD[b]	3,256 (13.4)	1.74 (1.67, 1.81)	<0.001	1.35 (1.29, 1.40)	<0.001	1.33 (1.28, 1.39)	<0.001

[a] Normal ($FEV_1/FVC \geq 0.7$ and $FVC \geq 80\%$ predicted), restricted ($FEV_1/FVC \geq 0.7$ and $FVC < 80\%$ predicted), GOLD I ($FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted), GOLD II ($FEV_1/FVC < 0.7$ and $50\% \leq FEV_1 < 80\%$ predicted), GOLD III ($FEV_1/FVC < 0.7$ and $30\% \leq FEV_1 < 50\%$ predicted), GOLD IV ($FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted). Normal was the reference group.
[b] Overall COPD was defined by $FEV_1/FVC < 0.7$, with non-COPD ($FEV_1/FVC \geq 0.7$) as the reference group.
[c] Mortality rate: per 1,000 person-years.
[d] Model 1 was adjusted for age, sex and city; Model 2 was further adjusted for education, body mass index, cigarette smoking, $PM_{2.5}$, occupational exposure, and calendar season and year; and Model 3 was further adjusted for alcohol consumption, physical activity, and vegetable and fruit intake.

Table 3
Associations between lung function and natural-cause mortality.

Lung function	Model 1[a] Hazard ratio (95%CI)	*P*	Model 2[a] Hazard ratio (95%CI)	*P*	Mode 3[a] Hazard ratio (95%CI)	*P*
FVC (L)	1.88 (1.84, 1.93)	<0.001	1.49 (1.45, 1.53)	<0.001	1.46 (1.42, 1.50)	<0.001
FEV_1 (L)	2.13 (2.07, 2.18)	<0.001	1.60 (1.56, 1.64)	<0.001	1.57 (1.53, 1.61)	<0.001
MMEF (L/s)	1.36 (1.34, 1.38)	<0.001	1.24 (1.22, 1.25)	<0.001	1.23 (1.21, 1.24)	<0.001
%Predicted FEV_1 (10%)	1.21 (1.20, 1.22)	<0.001	1.13 (1.12, 1.14)	<0.001	1.12 (1.12, 1.13)	<0.001

Abbreviations: FVC: forced vital capacity (L); FEV_1: forced expiratory volume in 1 s (L); MMEF: maximum mid-expiratory flow (L/s); and %predicted FEV_1: percentage predicted FEV_1 (%).
[a] Model 1 was adjusted for age, sex and city; Model 2 was further adjusted for education, body mass index, cigarette smoking, $PM_{2.5}$, occupational exposure, and calendar season and year; and Model 3 was further adjusted for alcohol consumption, physical activity, and vegetable and fruit intake.

Guo G et al. Respiratory Medicine 184 (2021) 106471

Effect of emphysema on mortality

- Emphysema was assessed with Low-dose CT scan in 9,047 subjects
- Age, pack-year, smoking status adjusted HR, 9.3

- **Extent of emphysema**

✓ Mild (1,908, 21%) : HR 3.2 (1.2-8.3)

✓ Moerate (512, 6%) : HR 22.3 (9.5-52.3)

✓ Marked (217, 2%) : HR 34.7 (13.69-86.6)

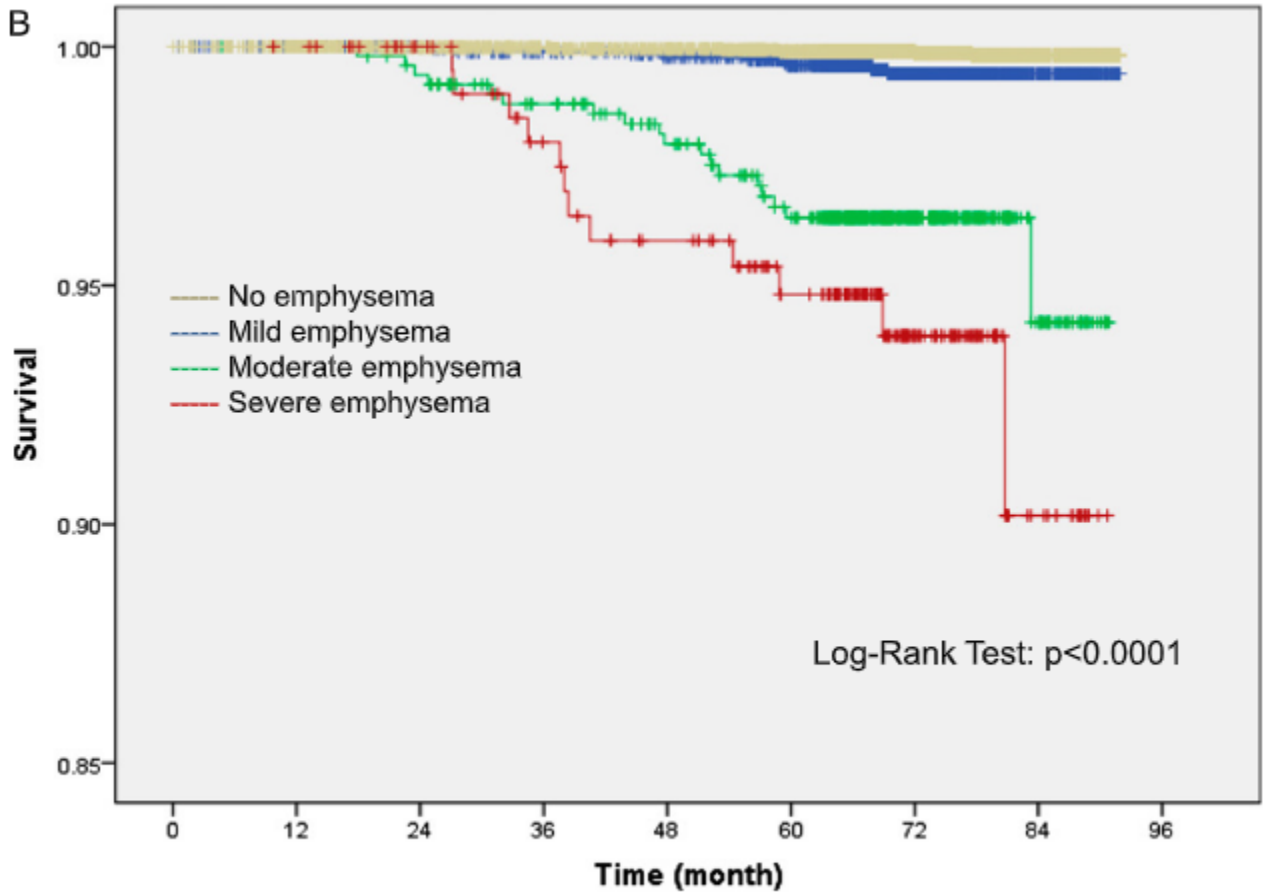


FIGURE 1. Kaplan-Meier curves showing an increase in the COPD-specific deaths for participants with emphysema on CT scans. A, Compared with those without emphysema B, As the extent of emphysema increases.

Zulueta JJ et al. CHEST 2012; 141(5):1216–1223

Risk of mortality depending on COPD phenotype

Copenhagen City Heart Study : respiratory and all cause mortality for 22 years

	Participants (n)	Respiratory mortality			All-cause mortality			Survival decrease†	
		Events (n [%])	Hazard ratio (95% CI)*	p value	Events (n [%])	Hazard ratio (95% CI)*	p value	Survival decrease (95% CI)	p value
Adjusted for age and sex	**8382**	**356 (7%)**			**3964 (50%)**				
Never-smokers without disease	2199	47 (3%)	1·00 (reference)		812 (41%)	1·00 (reference)		0·0 (reference)	
Ever-smokers without disease	5435	172 (5%)	1·90 (1·37–2·64)	0·0001	2598 (51%)	1·46 (1·35–1·58)	<0·0001	3·8 (3·0 to 4·5)	<0·0001
Asthma	158	11 (8%)	4·59 (2·38–8·86)	<0·0001	60 (39%)	1·40 (1·08–1·82)	0·01	3·3 (1·0 to 5·5)	0·004
COPD	320	46 (35%)	10·45 (6·88–15·88)	<0·0001	270 (87%)	2·76 (2·40–3·18)	<0·0001	10·1 (8·6 to 11·5)	<0·0001
ACO with early asthma onset	68	6 (12%)	8·17 (3·49–19·15)	<0·0001	38 (57%)	2·55 (1·84–3·53)	<0·0001	9·3 (5·4 to 13·1)	<0·0001
ACO with late asthma onset	202	74 (72%)	31·86 (21·94–46·28)	<0·0001	186 (93%)	3·72 (3·16–4·37)	<0·0001	12·8 (11·1 to 14·6)	<0·0001
Adjusted for age, sex, BMI, and FEV_1 % of predicted value	**8367**	**354 (6%)**			**3953 (50%)**				
Never-smokers without disease	2199	47 (3%)	1·00 (reference)		812 (41%)	1·00 (reference)		0·0 (reference)	
Ever-smokers without disease	5435	172 (5%)	1·66 (1·19–2·30)	0·003	2598 (51%)	1·37 (1·26–1·48)	<0·0001	3·0 (2·3 to 3·8)	<0·0001
Asthma	143	9 (7%)	2·58 (1·25–5·31)	0·01	49 (35%)	1·05 (0·79–1·41)	0·73	0·5 (−1·8 to 2·7)	0·67
COPD	320	46 (35%)	3·69 (2·34–5·83)	<0·0001	270 (87%)	1·75 (1·50–2·04)	<0·0001	5·4 (3·9 to 6·9)	<0·0001
ACO with early asthma onset	68	6 (12%)	2·30 (0·95–5·55)	0·06	38 (57%)	1·44 (1·03–2·01)	0·03	3·4 (−0·2 to 7·0)	0·06
ACO with late asthma onset	202	74 (72%)	6·36 (3·99–10·13)	<0·0001	186 (93%)	1·81 (1·50–2·17)	<0·0001	5·4 (3·6 to 7·2)	<0·0001
Adjusted for age, sex, BMI, and pack-years	**581**	**124 (42%)**			**485 (85%)**				
COPD	320	46 (35%)	1·00 (reference)		270 (87%)	1·00 (reference)		0·0 (reference)	
ACO with early asthma onset	67	6 (12%)	1·07 (0·45–2·57)	0·88	37 (56%)	0·99 (0·69–1·41)	0·94	0·0 (−3·4 to 3·4)	>0·99
ACO with late asthma onset	194	72 (77%)	3·51 (2·38–5·18)	<0·0001	178 (92%)	1·39 (1·14–1·69)	0·001	2·6 (1·0 to 4·2)	0·002

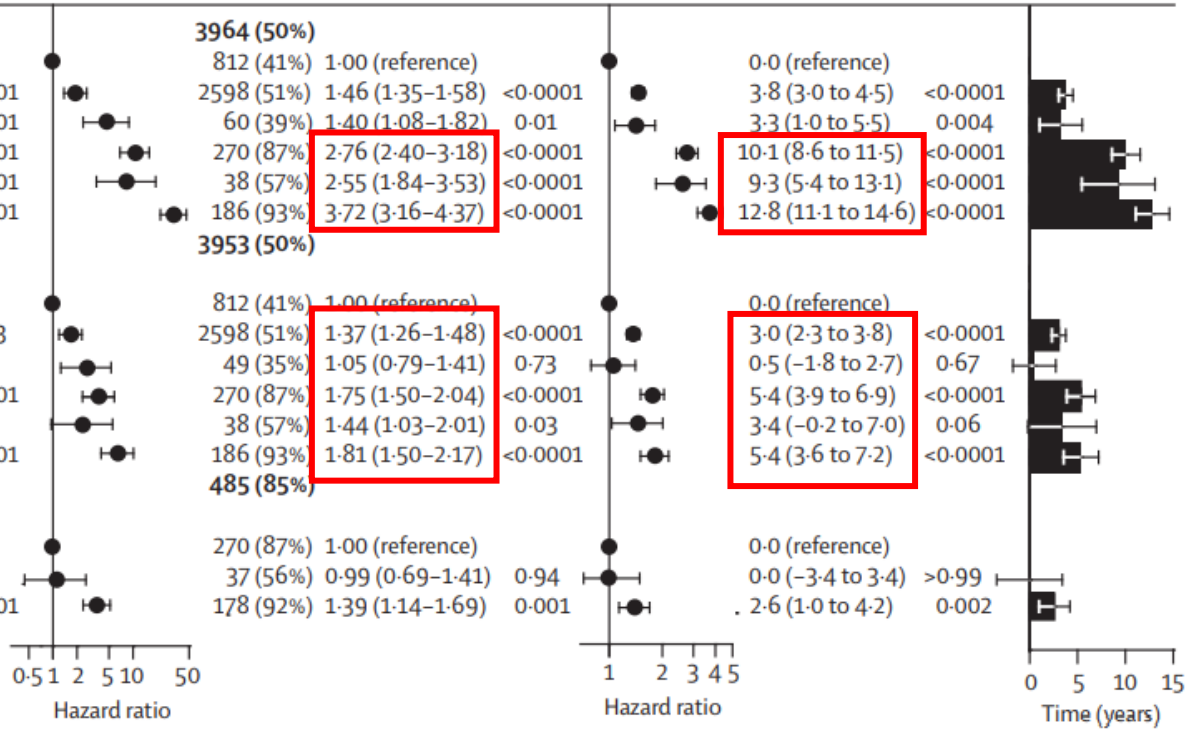
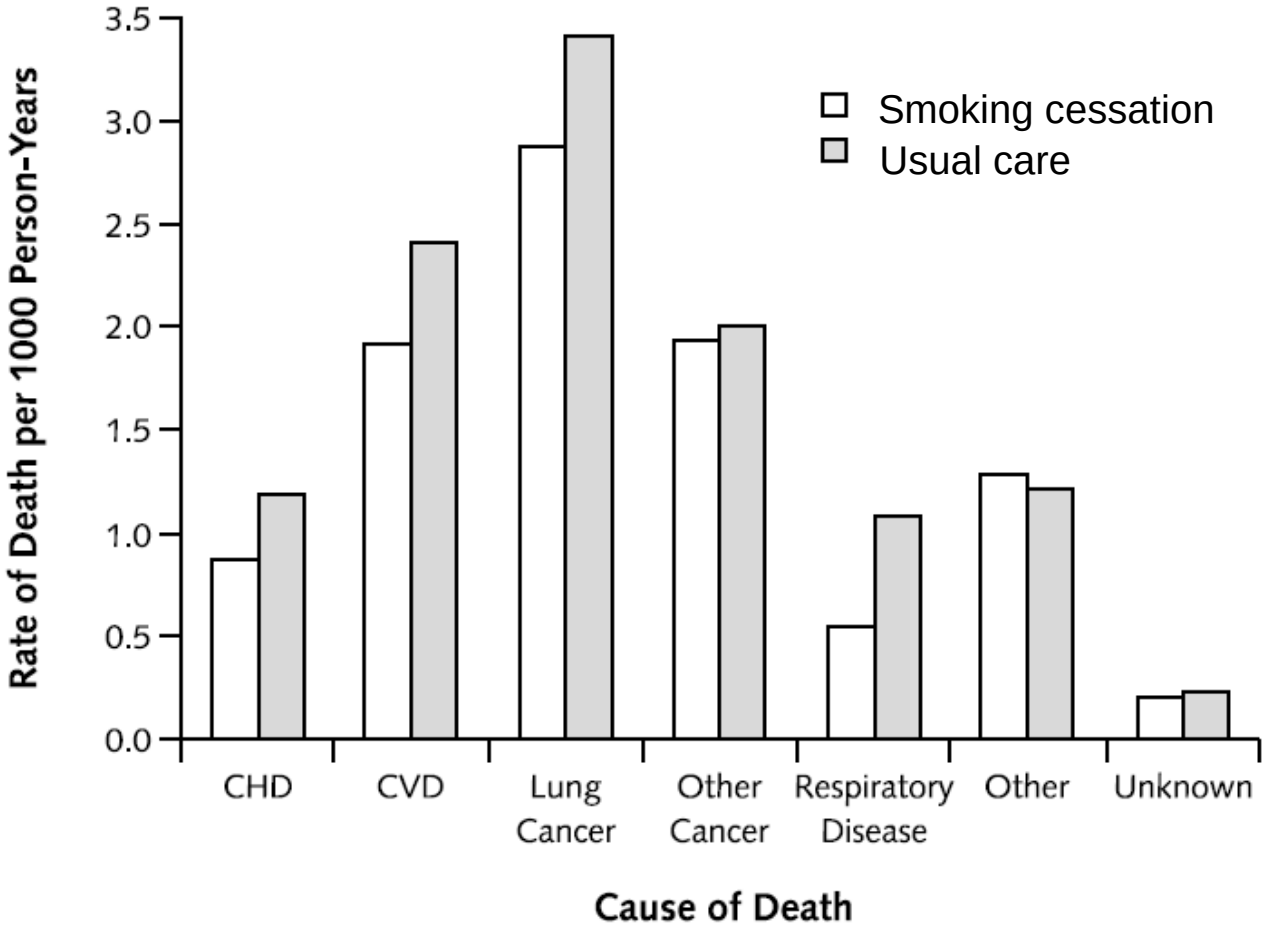


Figure 4: **Risk of respiratory and all-cause mortality and survival decrease in the six subgroups defined by smoking and presence of airway disease**
The x-axis is a log scale for respiratory and all-cause mortality. Percentages are Kaplan-Meier estimates. ACO=asthma-COPD overlap. BMI=body-mass index. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. *Estimated with Cox regression. *Estimated with Cox regression. †Bias-corrected bootstrap estimates based on Makuch-Ghali curves.

Lange P et al. Lancet Respir Med 2016; 4: 454–62

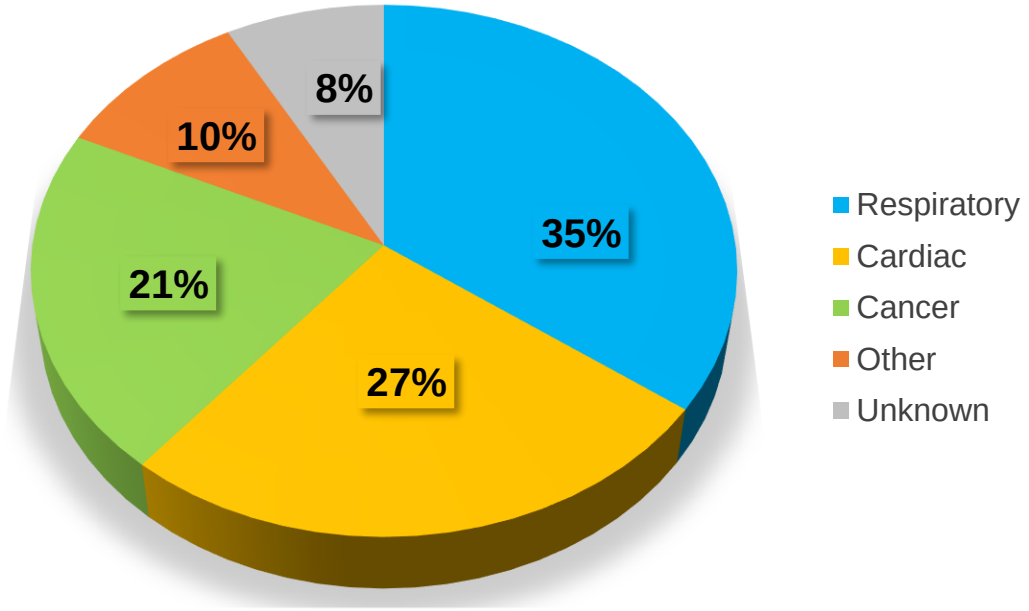
Causes of Death in COPD

Lung Health Study, 14.5 year mortality
Of total 5,887 patients, 731 died



Anthonisen NR et al. Ann Intern Med. 2005;142(4):233-9

TORCH causes of death
Of total 6,184 patients, 911 died



40% of death were definitely or probably related to COPD

Anthonisen NR et al. Ann Intern Med. 2005;142(4):233-9

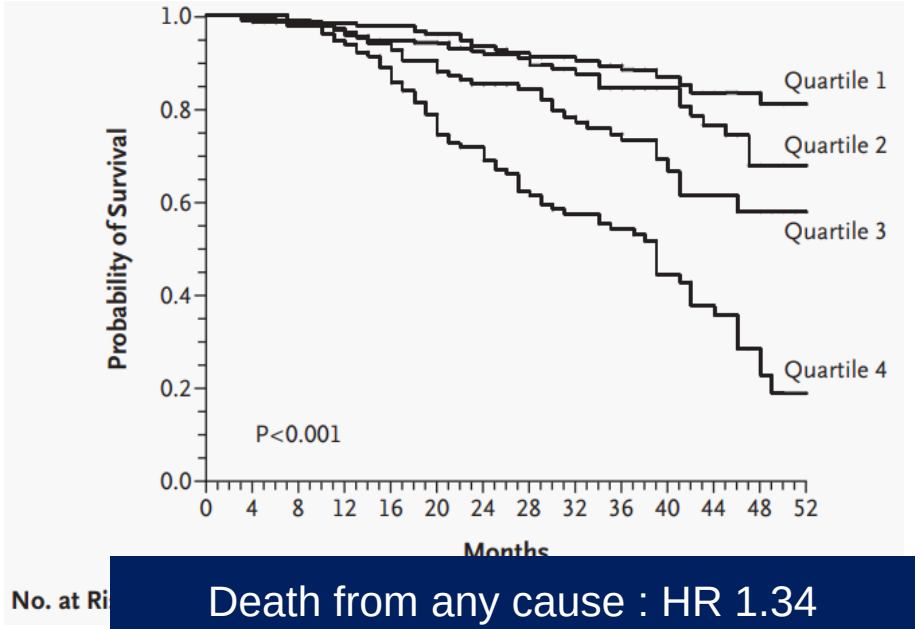
Personalized approaches to COPD: where are we ?

- For COPD related mortality : BODE index, CODEX index
- Acute exacerbation prediction tool
- Prediction of all-cause mortality by machine learning

BODE index : prediction tool for mortality and exacerbation

Variable / point	0	1	2	3
B : BMI	> 21	≤21		
O : FEV1 % pred	≥ 65	50-64	36-49	≤ 35
D : mMRC	0-1	2	3	4
E : 6MWD, m	≥ 350	250-349	150-249	≤149

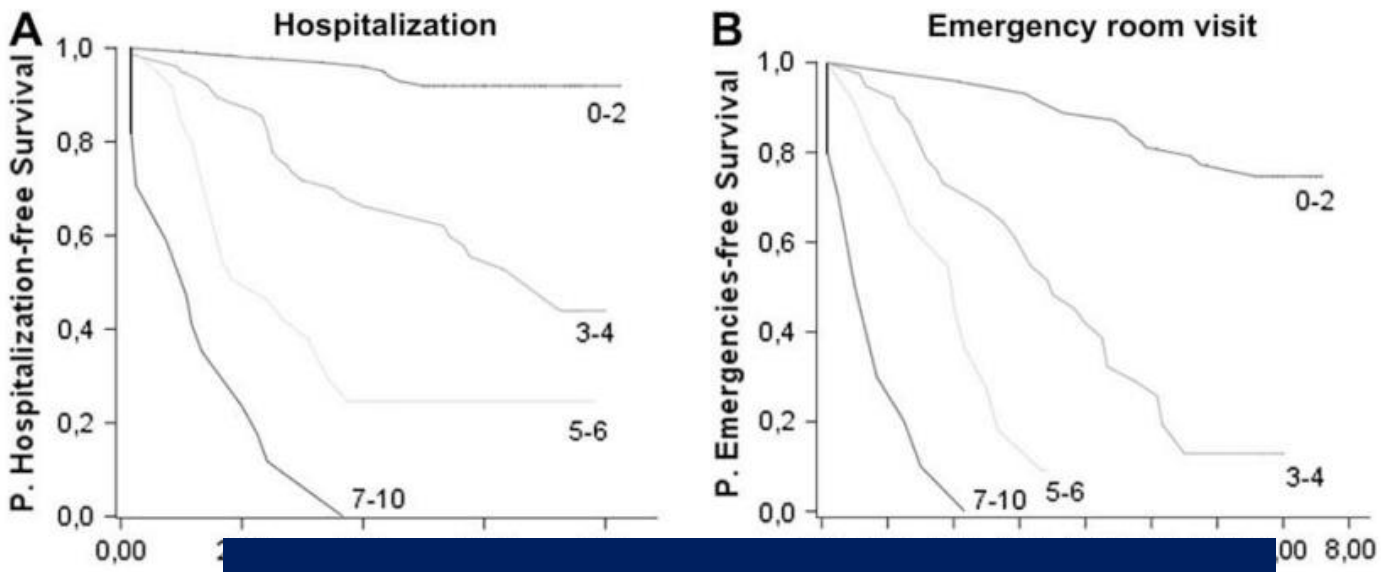
Prediction of mortality



Death from any cause : HR 1.34
Death from respiratory causes : HR 1.62

Celli BR et al. N Engl J Med 2004;350:1005-12

Prediction of risk of exacerbation

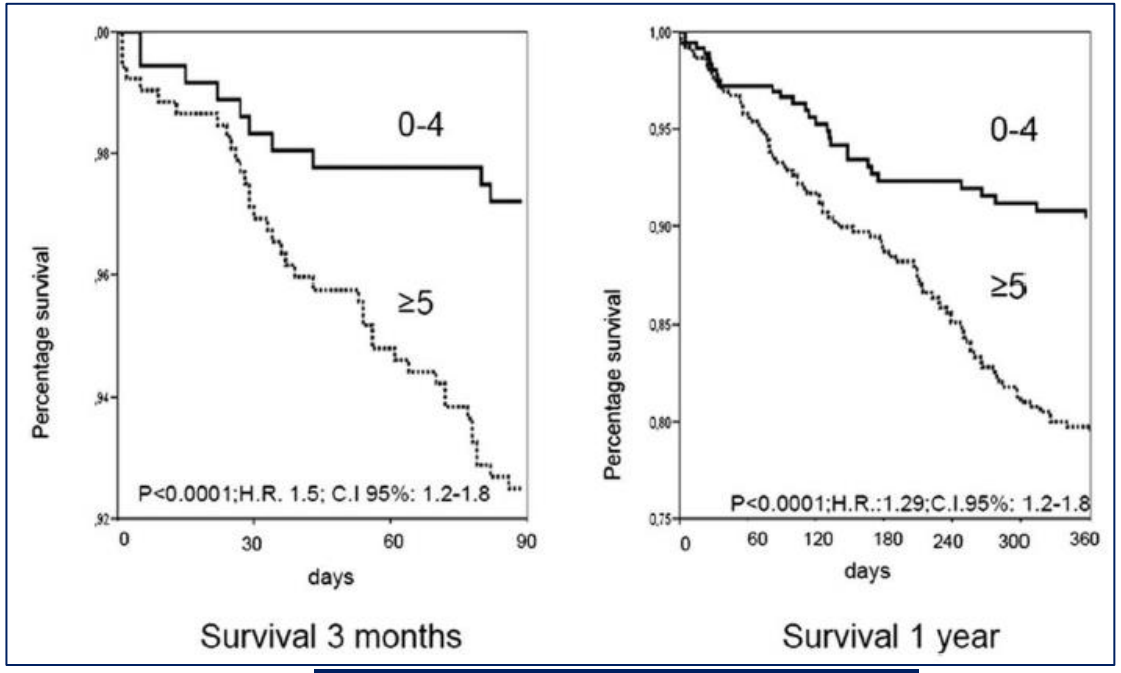


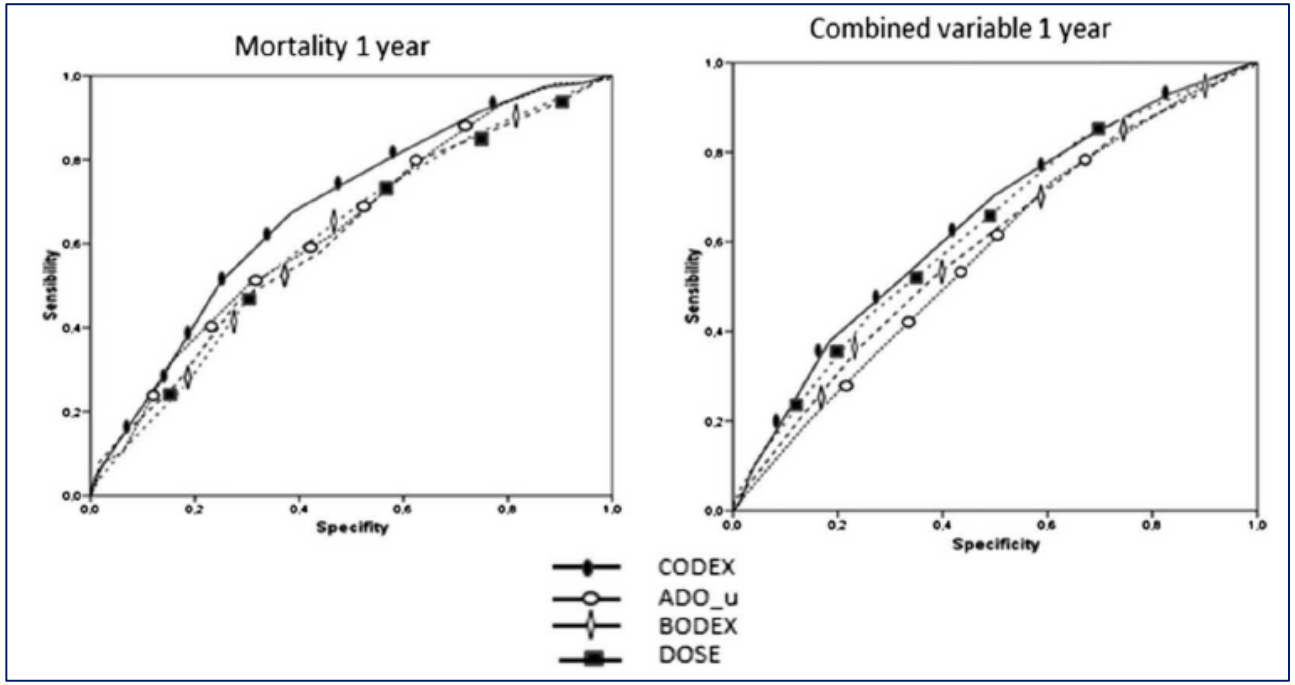
Mean time to the first exacerbation : 7.9, 5.7, 3.4 and 1.3 yrs for BODE index 0-2, 3-4, 5-6, and 7-10

Marin JM et al. Respiratory Medicine (2009) 103, 373-378

CODEX index : prediction tool for mortality and readmission

Variable / point	0	1	2	3
C : Charlson comorbidity index	0-4	5-7	≥8	
O : FEV1 % pred	≥ 65	50-64	36-49	≤ 35
D : mMRC	0-1	2	3	4
EX : Exacerbation	0	1-2	≥3	

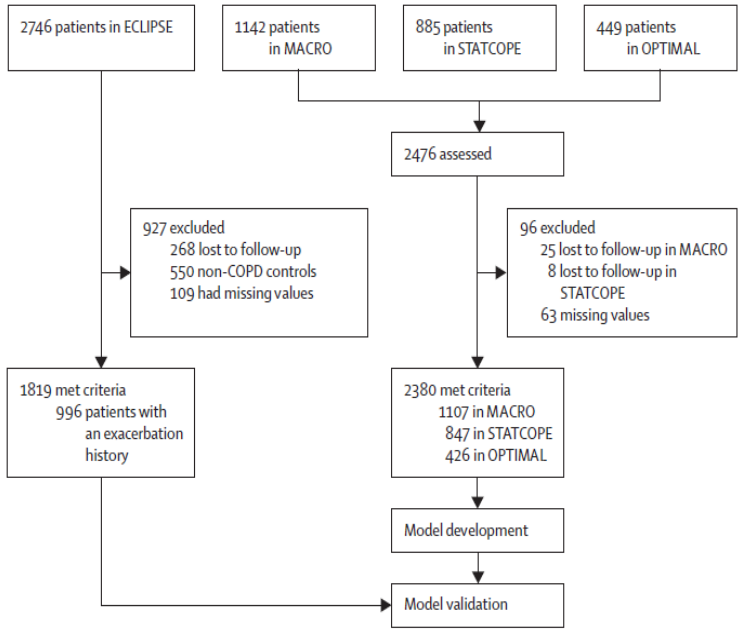




Mortality at 3mo : HR 1.5
Mortality at 1yr : HR 1.3

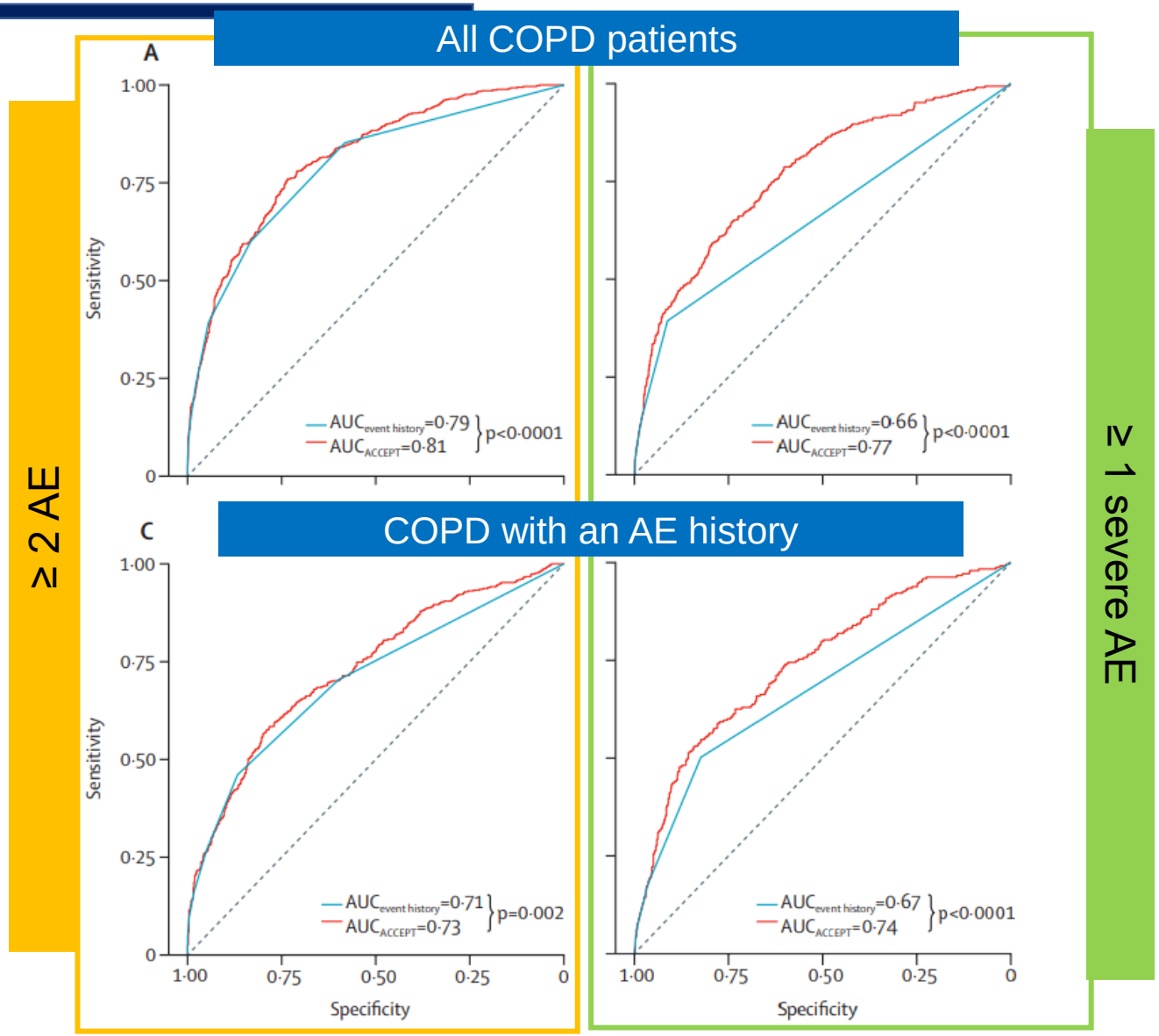
Almagro P et al. CHEST 2014; 145(5):972–980

The Acute COPD Exacerbation Prediction Tool (ACCEPT)



Predictor
Intercept
Male
Age at baseline (per 10–year)
Current smoker [b] at Baseline
Oxygen therapy [b] last year
Baseline FEV_1 (% predicted)
SGRQ Score [c] (per 10–unit)
BMI (per 10–unit)
CV-indicated statins [b]
LAMA [b]
LABA [b]
ICS [b]
Random Effect Variance
Random Effect Covariance

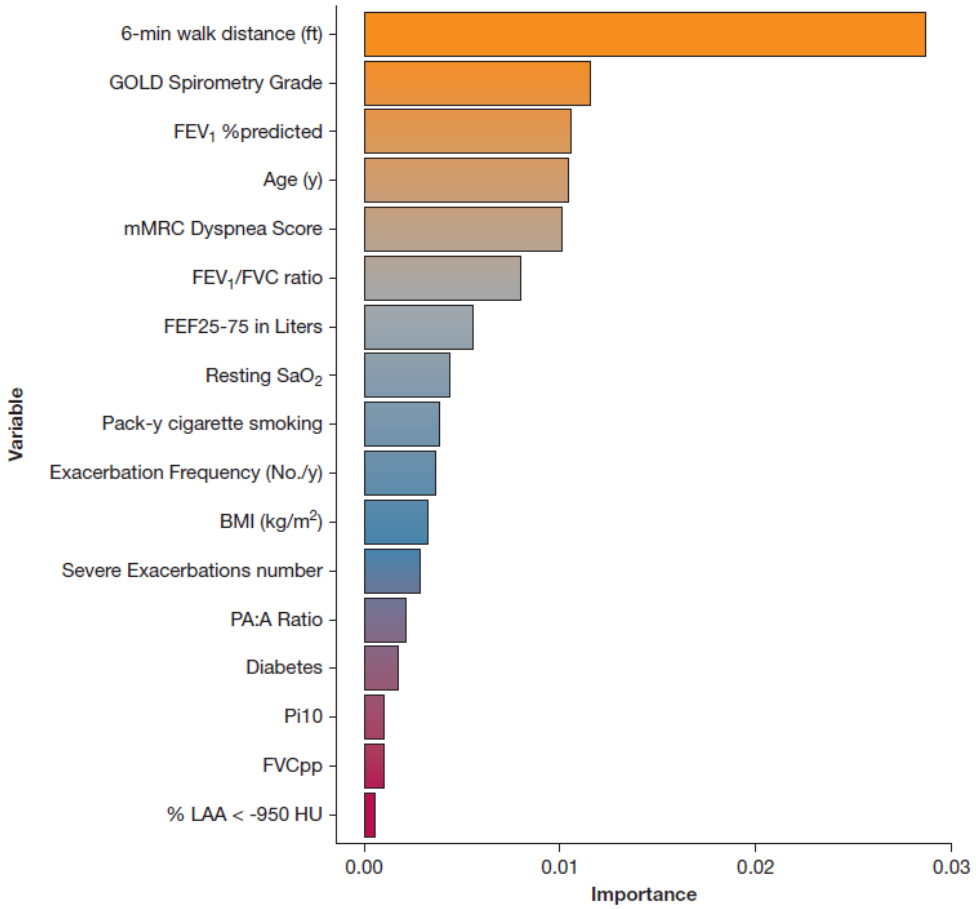
- **ACCEPT** showed **better performance for all exacerbations** regardless of severity compared to the predictive ability of "previous history of exacerbation"

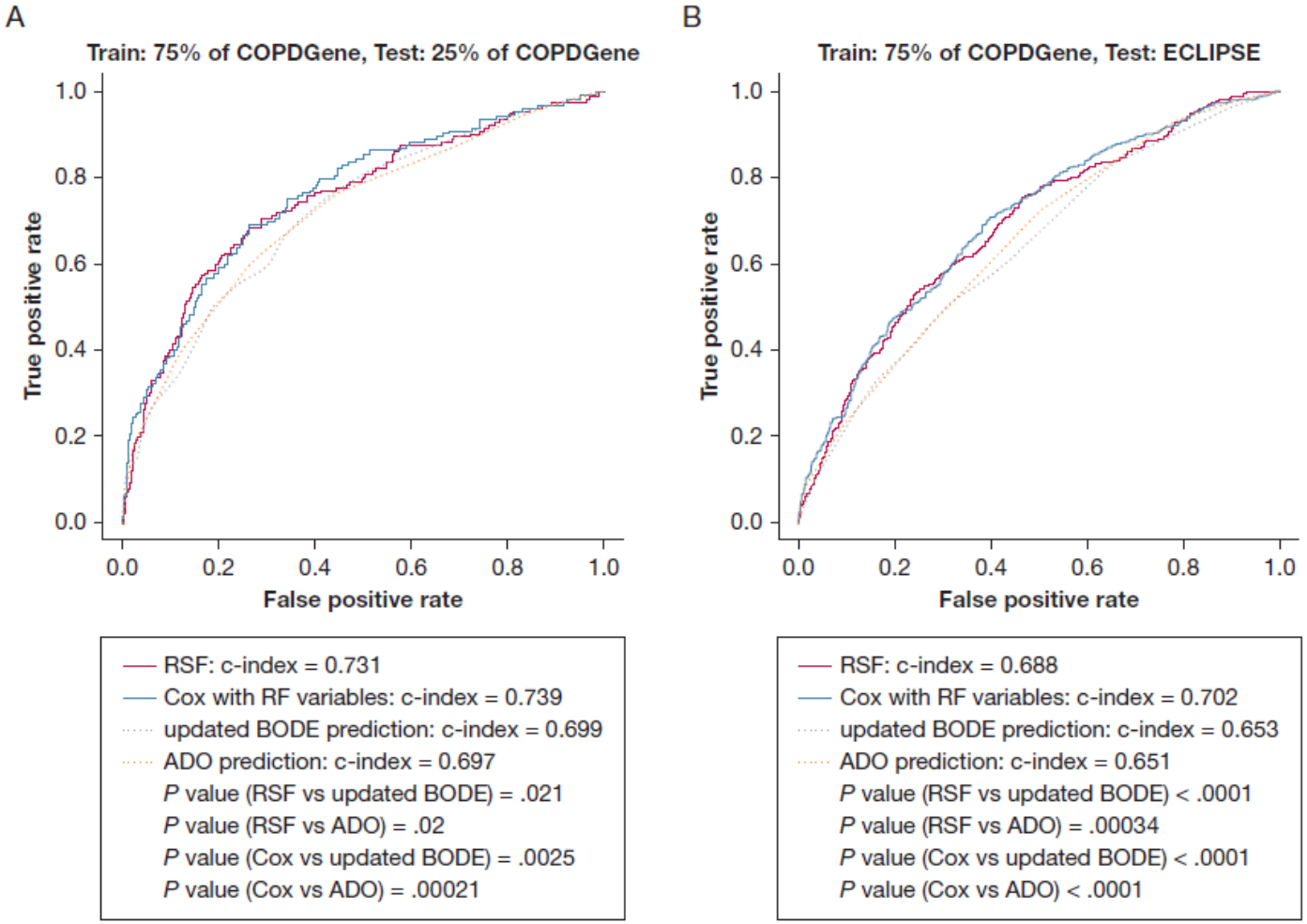


Adibi A et al. Lancet Respir Med. 2020;8(10):1013-1021.

Machine learning and prediction of mortality

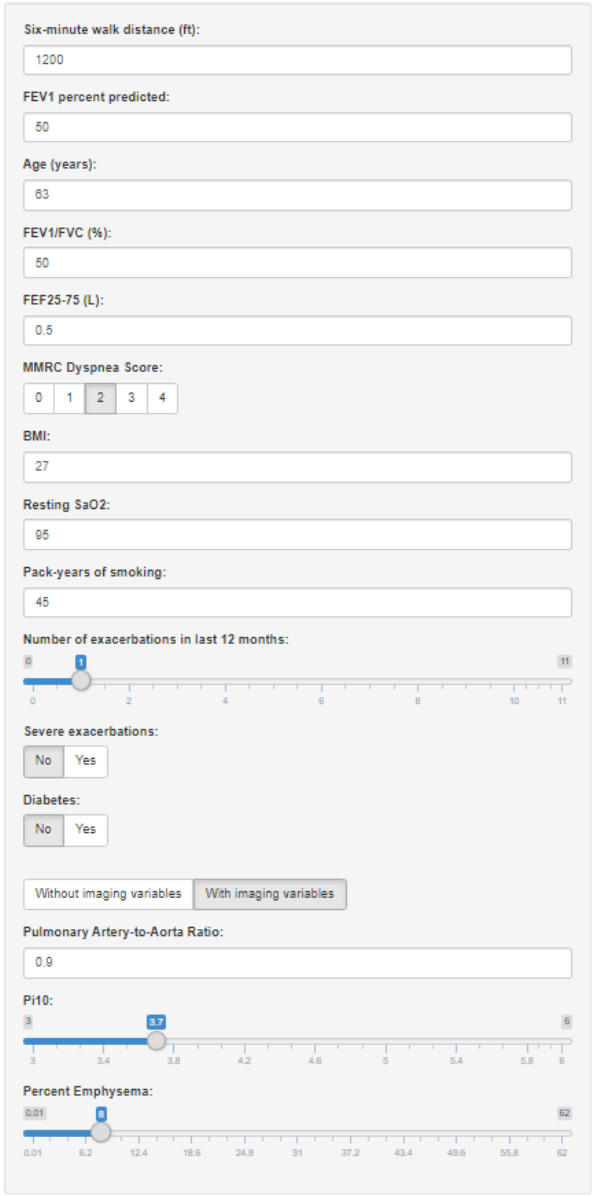
- Training cohort : COPDGene (n=1,974)
- Test cohort : COPDGene (n=658) & ECLIPSE (n=1,268)

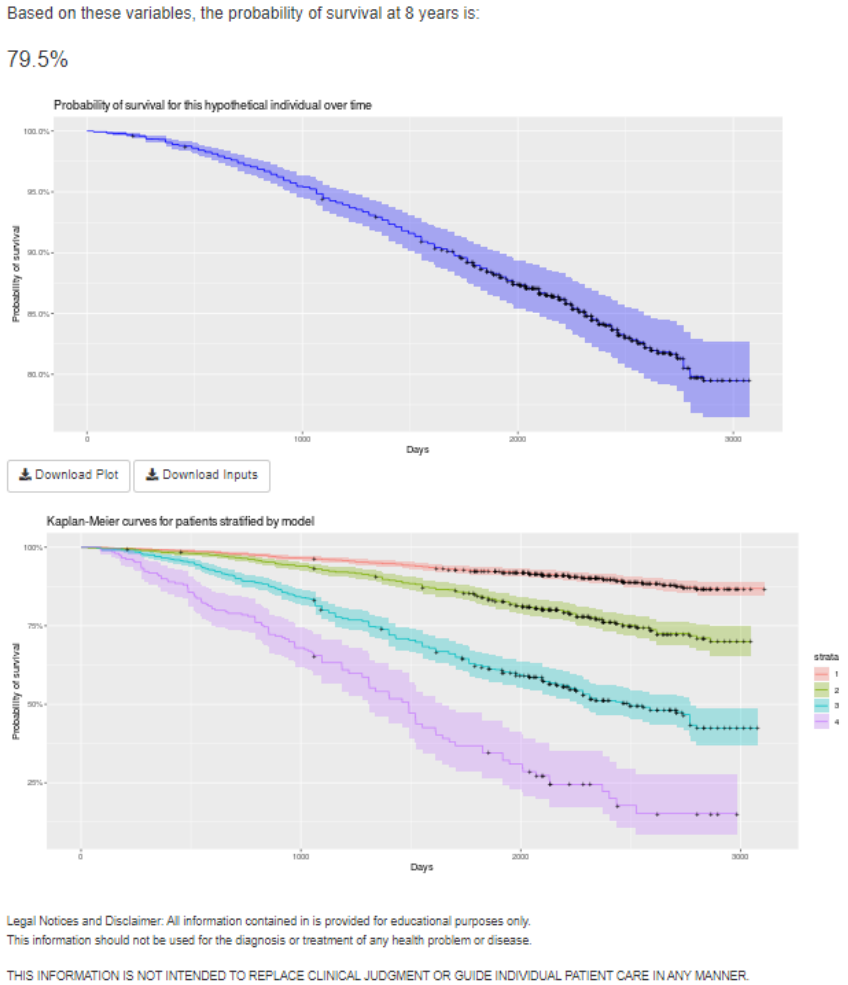




Moll M et al. CHEST 2020; 158(3):952-964

COPDGene Mortality Risk Calculator

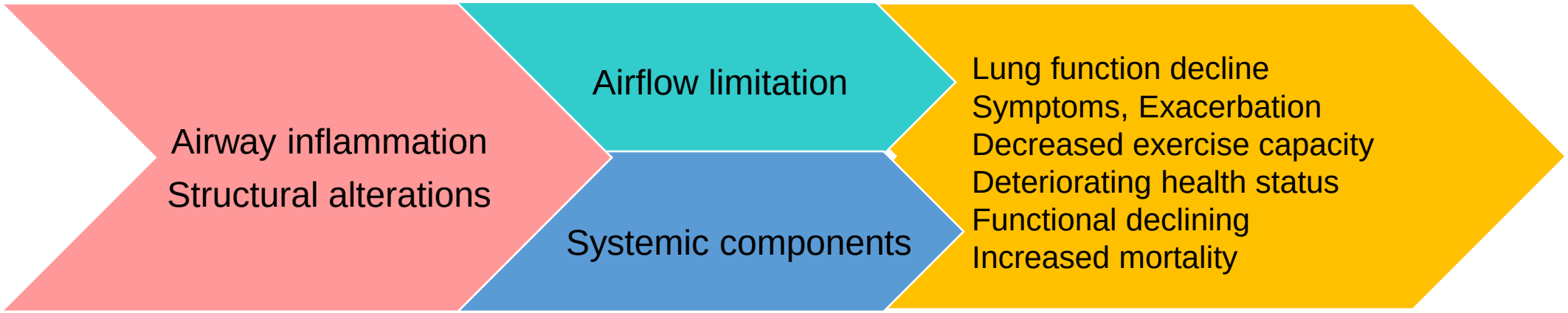




The model is available online at: https://cdnm.shinyapps.io/cgmortalityapp/.

Summary

- COPD is a progressive and multicomponent disease
- Pulmonary and extra-pulmonary manifestations contribute to course of COPD



- The treatment of COPD is no longer focused exclusively on inhaled therapy but is taking on multidimensional approach.

Thank you
for your attention !